PATENT APPLICATION

MODULATORS OF ANGIOGENESIS AND TUMORIGENESIS

Inventor(s):

James B. Lorens, a citizen of the United States, residing at
Kraakenesveien 10
N-5152 Bønes NORWAY

Robert E. Atchison, a citizen of the United States, residing at
631 O'Farrell St., #911
San Francisco, CA 94109

Anabella Friera, a citizen of the United States, residing at
229 Carmelo Lane
South San Francisco, CA 94080

Sacha Holland, a citizen of the United Kingdom, residing at
518 Foerster Street, Apt. B
San Francisco, CA 94127

Assignee:

Rigel Pharmaceuticals, Incorporated
1180 Veterans Blvd.
South San Francisco, CA 94080

Entity: Small business concern

MODULATORS OF ANGIOGENESIS AND TUMORIGENESIS

CROSS-REFERENCES TO RELATED APPLICATIONS

The present application claims priority to USSN 60/421,989, filed October

5   29, 2002, and USSN 60/_____, TTC Ref. No. 021044-005810, filed October 17, 2003,

each herein incorporated by reference in their entirety.

STATEMENT AS TO RIGHTS TO INVENTIONS MADE UNDER
FEDERALLY SPONSORED RESEARCH AND DEVELOPMENT

10   Not applicable.

FIELD OF THE INVENTION

The present invention relates to regulation of angiogenesis and

tumorigenesis. The invention further relates to methods for identifying and using agents,

15   including small organic molecules, antibodies, peptides, cyclic peptides, nucleic acids,

antisense nucleic acids, RNAi, and ribozymes, that modulate angiogenesis and

tumorigenesis via modulation of endothelial cell haptotaxis; as well as to the use of

expression profiles and compositions in diagnosis and therapy of angiogenesis and

cancer.

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BACKGROUND OF THE INVENTION

The migration of activated endothelial cells through a vitronectin-rich

provisional matrix is critical to the formation of new blood vessels during angiogenesis

and is dependent on adhesion receptors containing alphav integrins (such as alphavbeta3

25   which binds to vitronectin). Peptide and antibody inhibitors of alphavbeta3 integrin

inhibit tumor growth *in vivo*.

Angiogenesis is typically limited in a normal adult to the placenta, ovary,

endometrium and sites of wound healing. However, angiogenesis, or its absence, plays

an important role in the maintenance of a variety of pathological states. Some of these

30   states are characterized by neovascularization, e.g., cancer and tumorigenesis, e.g.,

endometriosis, diabetic retinopathy, glaucoma, glomerulonephritis, and age related

macular degeneration. Others, e.g., stroke, infertility, heart disease, e.g., restenosis,

ulcers, and scleroderma, are diseases of angiogenic insufficiency. Therefore, there is a

need to identify nucleic acids encoding proteins involved in the regulation of angiogenesis and tumorigenesis, to identify, e.g., modulators of angiogenesis, as well as new therapeutic and diagnostic applications.

5 SUMMARY OF THE INVENTION

Novel targets for anti-angiogenic and anti-tumorigenic therapy have been identified using a functional genetic screen based on endothelial cell haptotaxis. Inhibition or activation of these targets (by small molecule inhibitors; protein, antibody and peptide therapeutics; RNAi; antisense; gene therapy etc.) have therapeutic value in

10 modulating angiogenesis and tumorigenesis,, e.g., breast, lung, colon, ovarian, liver, thyroid, stomach, bladder, and prostate cancer, basal cell carcinoma, melanoma, lymphomas, leukemias, e.g., myeloid leukemia (CML and AML), endometriosis, diabetic retinopathy, glaucoma, glomerulonephritis, age related macular degeneration, as well as, e.g., stroke, infertility, heart disease, e.g., restenosis, ulcers, and scleroderma.

15 The present invention therefore provides nucleic acids encoding proteins involved in modulation of vitronectin induced endothelial cell haptotaxis and modulation of angiogenesis and tumorigenesis. The invention therefore provides methods of screening for compounds, e.g., small organic molecules, antibodies, nucleic acids, peptides, cyclic peptides, nucleic acids, antisense molecules, RNAi, and ribozymes, that

20 are capable of modulating angiogenesis or tumorigenesis, e.g., either activating or inhibiting angiogenesis or tumorigenesis. Therapeutic and diagnostic methods and reagents are also provided.

In one aspect, the present invention provides a method for identifying a compound that modulates angiogenesis and tumorigenesis, the method comprising the

25 steps of: (i) contacting the compound with an angiogenesis or tumorigenesis modulating polypeptide or fragment thereof, the polypeptide encoded by a nucleic acid that hybridizes under stringent conditions to a reference nucleic acid encoding the polypeptide, the polypeptide selected from the group consisting of Axl, tubulin cofactor D, transglutaminase 2, cytosine deaminase, peptidase M41 (paraplegin), CD13

30 aminopeptidase, PRK-1, zip kinase, Gas6, SRm160, non-muscle myosin heavy chain, calmodulin 2, novel symporter, novel semaphorin, novel zinc finger helicase (FLJ22611), plexin-A2, deoxycytidylate deaminase, and a novel sugar transporter; and (ii) determining the functional effect of the compound upon the polypeptide.

In one embodiment, the functional effect is determined *in vitro*. In another embodiment, the functional effect is a physical effect. In another embodiment, the functional effect is determined by measuring ligand binding to the polypeptide. In another embodiment, the functional effect is a chemical effect.

In one embodiment, the polypeptide is expressed in a eukaryotic host cell. In another embodiment, the functional effect is a physical effect. In another embodiment, the functional effect is determined by measuring ligand binding to the polypeptide. In another embodiment, the functional effect is a chemical or phenotypic effect. In another embodiment, the polypeptide is expressed in a eukaryotic host cell, e.g., an endothelial cell. In another embodiment, the functional effect is determined by measuring $\alpha v \beta 3$ expression, haptotaxis, tumor cell proliferation, or tumor growth *in vivo*.

In one embodiment, modulation is inhibition of angiogenesis or tumorigenesis.

In one embodiment, the polypeptide is recombinant.

In one embodiment, the compound is an antibody, a peptide, an antisense molecule, a RNAi molecule, or a small organic molecule.

In another aspect, the present invention provides a method for identifying a compound that modulates tumorigenesis or angiogenesis, the method comprising the steps of (i) contacting the compound with an angiogenesis or tumorigenesis modulating polypeptide or fragment or inactive variant thereof, the polypeptide selected from the group consisting of Axl, tubulin cofactor D, transglutaminase 2, cytosine deaminase, peptidase M41 (paraplegin), CD13 aminopeptidase, PRK-1, zip kinase, Gas6, SRm160, non-muscle myosin heavy chain, calmodulin 2, novel symporter, novel semaphorin, novel zinc finger helicase (FLJ22611), plexin-A2, deoxycytidylate deaminase, and a novel sugar transporter (ii) determining the physical effect of the compound upon the polypeptide or fragment thereof or inactive variant thereof; and (iii) determining the chemical or phenotypic effect of the compound upon a cell comprising the polypeptide or fragment thereof or inactive variant thereof, thereby identifying a compound that modulates tumorigenesis or angiogenesis.

In another aspect, the present invention provides a method of modulating angiogenesis or tumorigenesis in a subject, the method comprising the step of administering to the subject a therapeutically effective amount of a compound identified using the methods described herein.

In one embodiment, the subject is a human.

In one embodiment, the compound is an antibody, an antisense molecule, a peptide, or an RNAi molecule, or a small organic molecule.

In one embodiment, the compound inhibits angiogenesis or tumorigenesis.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 shows a screening protocol for haptotactic migration inhibitors.

Figure 2 shows a cellomics haptotaxis assay.

Figure 3 shows that a CD13/N-aminiopeptidase is involved in haptotaxis.

Figure 4 shows that a transgluaminase II protein is involved in haptotaxis.

Figure 5 shows that a zip kinase protein is involved in haptotaxis.

Figure 6 shows that a PRK-1 protein is involved in haptotaxis.

Figure 7 shows that PRK1 mRNA is expressed in endothelial cells and PBMCs.

Figure 8 shows that a PRK-1 protein is involved in haptotaxis and $\alpha v\beta 3$ expression.

Figure 9 shows that PRK-1 RNAi reduces PRK-1 message, haptotaxis and $\alpha v\beta 3$ expression.

Figure 10 shows that PRK-1 RNAi reduces tube formation in a co-culture assay.

Figure 11 shows that Ax1 and Gas6 are involved in haptotaxis.

Figure 12 shows that Axl RNAi reduces Axl mRNA expression.

Figure 13 shows that Axl RNAi inhibit haptotaxis to vitronectin.

Figure 14 shows that Axl RNAi reduces Axl protein expression.

Figure 15 shows that Axl RNAi inhibits vitronectin haptotaxis and HUVEC proliferation.

Figure 16 shows that an Axl extracellular domain was isolated in a VEGF-R2 screen.

Figure 17 shows that Axl RNAi inhibits tube formation in a co-culture assay.

Figure 18 shows a sponge angiogenesis/xenograft model.

Figure 19 shows that a deoxycytidylate deaminase is involved in angiogenesis.

Figure 20 shows that a plexin-A2 is involved in angiogenesis.

DETAILED DESCRIPTION OF THE INVENTION

Introduction

We have used a functional genetic screening strategy to identify proteins involved in regulating endothelial cell migration on specific matrix components, e.g.

5   vitronectin. Using a retroviral-based system, we have stably expressed complex libraries of various types of genetic elements (e.g. cDNAs and GFP-fusions) in human primary endothelial cells (e.g. HUVECs). Starting with early passage primary endothelial cells representing an "angiogenic state" (i.e., proliferative, highly motile), single cells that have switched to a more differentiated "angiostatic state" (i.e., quiescent, reduced motility) can

10   be identified. In order to focus on the migration step of the angiogenic cycle, conditions were established which allowed highly efficient migration of HUVEC cells along a haptotactic gradient of specific matrix proteins (e.g. vitronectin / fibronectin) in a Boyden chamber assay. Large populations of HUVEC cells were then infected with a GFP-fused cDNA library and selected for impaired haptotaxis. Additional assays for proteins

15   involved in angiogenesis and tumorigenesis include a VEGFR2 assay, a HUVEC/smooth muscle cell co-culture assay for endothelial tube formation, chemo-invasion assays, and tumor cell proliferation assays. Finally, human/mouse tumor xenograft assays, mouse sponge angiogenesis and tumorigenesis assays (sponge with human ECs +/- human tumor cells in SCID mice), a collagen-antibody induced arthritis model for RA, and retinal

20   neovascularization assays can be used to identify angiogenesis and tumorigenesis proteins *in vivo* and to assay for modulators of such proteins.

The angiogenesis and tumorigenesis proteins identified using the haptotaxis assay described herein, e.g., Axl, its ligand, Gas6, tubulin cofactor D, transglutaminase 2, cytosine deaminase, plexin-A2, peptidase M41 (paraplegin), CD13

25   aminopeptidase, PRK-1, zip kinase, SRm160, non-muscle myosin heavy chain, calmodulin 2, novel symporter, novel semaphorin, novel zinc finger helicase (FLJ22611), and a novel sugar transporter, therefore represent targets for the development of angiogenic drugs, preferably anti-angiogenic drugs, e.g., anti-angiogenic drugs for treatment of neovascularization, e.g., cancer, diabetic retinopathy, endometriosis,

30   glomerulonephritis, restenosis, glaucoma, rheumatoid arthritis, and age related macular degeneration, or angiogenic drugs for treatment of angiogenic insufficiency, e.g., stroke, infertility, heart disease, ulcers, and scleroderma. Modulators include small organic molecules, nucleic acids, peptides, cyclic peptides, antibodies, antisense molecules, RNAi molecules, and ribozymes. The nucleic acids and proteins of the invention are also useful

for diagnostic applications, using, e.g., nucleic acid probes, oligonucleotides, and antibodies. These polypeptides are also involved in tumorigenesis and cellular proliferation, and are useful for the development of therapeutic molecules to treat diseases associated with angiogenesis, tumorigenesis, and cellular proliferation. Furthermore, the

5   polypeptides described herein and the nucleic acids encoding them are useful for diagnostic assays for diseases associated with angiogenesis, tumorigenesis, and cellular proliferation.

In one embodiment, the protein Axl is involved in angiogenesis, tumorigenesis, and cellular proliferation. Axl is a receptor tyrosine kinase that posses

10   transforming activity *in vitro*. Axl is activated by its ligand, Gas 6. Axl, Sky, and Mer form a family of receptor tyrosine kinases that are activated by Gas6. Axl is expressed in myeloid cell types and vasculature, e.g., endothelial cells (HUVEC), VSMC, monocytes, macrophages, CD34+ cells, bronchial epithelium, breast epithelium, neurons, and chondrocytes. Axl is upregulated in VSMC after vascular injury. Gas6-Axl interactions

15   stimulate cell survival and chemotaxis. Knockout and transgenic mice for Axl show no overt phenotypes. Axl is associated with several diseases, including rheumatoid arthritis (O'Donnell *et al., Am. J. Pathol.* 154:1171-1180 (1999)), endometriosis (Sun *et al., Mol. Human Reproduction* 8:552-559 (2002)), cancer, e.g. myeloid leukemias such as AML and CML, thyroid carcinomas, and breast cancer. Axl can be activated using antibody

20   crosslinking, pervanadate, or Gas6.

In another embodiment, the protein PRK-1 is involved in angiogenesis and tumorigenesis. PRK-1 is a cytoplasmic serine/threonine kinase related to PKC. PRK-1 binds Rho GTPase through the N-terminus and is regulated by activation loop phosphorylation by PD-1. PRK activation by PDK1 is Rho-dependent and membrane

25   localized. PRK-1 I exhibits elevated expression in endothelial cells and PBMC. PRK-1 is upregulated in breast and prostate epithelial carcinoma cells as compared to normal cells and activates androgen receptor signaling (*see, e.g.*, Metzger *et al., EMBO J.* 22:270-280 (2003)). PRK-1 RNAi inhibits PRK-1 protein and VN and FN haptotaxis, (including a PRK-1 3' UTR RNAi and a PRK-1 RNAi vector). PRK-1 RNAi reduces

30   tube formation in the co-culture assays, as well as SDF-1 and VEGF chemotaxis in HUVECs. PRK-1 RNAi inhibits vitronectin-induced haptotaxis in PASMCs. Expression of kinase inactive PRK-1 in HUVECs increases vitronectin haptotaxis. The PRK-1 screening hit GH1-54 co-immunoprecipitates with full-length PRK-1. *In vitro* kinase

assays with PRK-1 can be used to assay for PRK-1 modulators and thus for modulators of angiogenesis.

In another embodiment, the protein PRK-2 is involved in angiogenesis and tumorigenesis. PRK-2 is widely expressed in adherent cell types. PRK-2 siRNA inhibits vitronectin-induced haptotaxis in HUVECs and PASMCs and also inhibits PRK-2 protein expression. In another embodiment, the proteins deoxycytidylate deaminase (sense hit) (, transglutaminase II (antisense hit), plexin-A2 (sense hit), and ZIP-kinase/DAP kinase 3 (sense 3' UTR hit), are involved in angiogenesis and tumorigenesis. ZIP kinase exhibits a restricted tissue expression pattern and is highly expressed in hepatocytes. ZIP kinase RNAi inhibits VN haptotaxis.

Definitions

By "disorder associated with angiogenesis or tumorigenesis" or "disease associated with angiogenesis or tumorigenesis" herein is meant a disease state which is marked by either an excess or a deficit of vessel development. Angiogenesis and tumorigenesis disorders associated with increased angiogenesis include, but are not limited to, breast, lung, colon, ovarian, liver, stomach, bladder, thyroid, and prostate cancer, basal cell carcinoma, melanoma, lymphomas, leukemias, e.g., myeloid leukemia (AML, CML), endometriosis, diabetic retinopathy, glaucoma, glomerulonephritis, rheumatoid arthritis, and age related macular degeneration. Pathological states for which it may be desirable to increase angiogenesis include stroke, infertility, heart disease, e.g., restenosis, ulcers, and scleroderma. An increase in angiogenesis may also be desirable in transplantation or for artificial or *in vitro* growth of organs.

By "disorder associated with cellular proliferation or tumorigenesis" or "disease associated with cellular proliferation or tumorigenesis" herein is meant a disease state which is marked by either an excess or a deficit of cellular proliferation or apoptosis. Such disorders associated with increased cellular proliferation include, but are not limited to, cancer and non-cancerous pathological proliferation.

The terms "angiogenesis and/or tumorigenesis polypeptide" or a nucleic acid encoding an "angiogenesis and/or tumorigenesis polypeptide" refer to nucleic acid and polypeptide polymorphic variants, alleles, mutants, and interspecies homologs that: (1) have an amino acid sequence that has greater than about 60% amino acid sequence identity, 65%, 70%, 75%, 80%, 85%, 90%, preferably 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% or greater amino acid sequence identity, preferably over a region of

over a region of at least about 25, 50, 100, 200, 500, 1000, or more amino acids, to a polypeptide encoded by a referenced nucleic acid or an amino acid sequence described herein; (2) specifically bind to antibodies, e.g., polyclonal antibodies, raised against an immunogen comprising a referenced amino acid sequence, immunogenic fragments

5   thereof, and conservatively modified variants thereof; (3) specifically hybridize under stringent hybridization conditions to a nucleic acid encoding a referenced amino acid sequence, and conservatively modified variants thereof; (4) have a nucleic acid sequence that has greater than about 95%, preferably greater than about 96%, 97%, 98%, 99%, or higher nucleotide sequence identity, preferably over a region of at least about 25, 50, 100,

10   200, 500, 1000, or more nucleotides, to a reference nucleic acid sequence. A polynucleotide or polypeptide sequence is typically from a mammal including, but not limited to, primate, e.g., human; rodent, e.g., rat, mouse, hamster; cow, pig, horse, sheep, or any mammal. The nucleic acids and proteins of the invention include both naturally occurring or recombinant molecules.

15   The phrase "functional effects" in the context of assays for testing compounds that modulate activity of an angiogenesis and tumorigenesis protein includes the determination of a parameter that is indirectly or directly under the influence of an angiogenesis polypeptide, e.g., a chemical or phenotypic effect such as loss-of angiogenesis or tumorigenesis phenotype represented by a change in expression of a cell

20   surface marker $\alpha v\beta 3$ integrin, changes in cellular migration, changes in endothelial tube formation, and changes in tumor growth, or changes in cellular proliferation, especially endothelial cell proliferation; or enzymatic activity; or, e.g., a physical effect such as ligand binding or inhibition of ligand binding. A functional effect therefore includes ligand binding activity, the ability of cells to proliferate, expression in cells undergoing

25   angiogenesis or tumorigenesis, and other characteristics of angiogenic and tumorigenic cells. "Functional effects" include *in vitro*, *in vivo*, and *ex vivo* activities.

        By "determining the functional effect" is meant assaying for a compound that increases or decreases a parameter that is indirectly or directly under the influence of an angiogenesis protein, e.g., measuring physical and chemical or phenotypic effects.

30   Such functional effects can be measured by any means known to those skilled in the art, e.g., changes in spectroscopic characteristics (e.g., fluorescence, absorbance, refractive index); hydrodynamic (e.g., shape), chromatographic; or solubility properties for the protein; ligand binding assays, e.g., binding to antibodies; measuring inducible markers or transcriptional activation of the angiogenesis protein; measuring changes in enzymatic

activity; the ability to increase or decrease cellular proliferation, apoptosis, cell cycle arrest, measuring changes in cell surface markers, e.g., $\alpha v\beta 3$ integrin; and measuring cellular proliferation, particularly endothelial cell proliferation. Determination of the functional effect of a compound on angiogenesis or tumorigenesis can also be performed

5   using assays known to those of skill in the art such as endothelial cell tube formation assays; haptotaxis assays; the chick CAM assay; the mouse corneal assay; VEGF receptor assays, co-culture tube formation assays, and assays that assess vascularization of an implanted tumor. Tumorigenesis can be measured using *in vivo* mouse models such as a xenograft model. The functional effects can be evaluated by many means known to those

10   skilled in the art, e.g., microscopy for quantitative or qualitative measures of alterations in morphological features, e.g., tube or blood vessel formation, measurement of changes in RNA or protein levels for angiogenesis-associated sequences, measurement of RNA stability, identification of downstream or reporter gene expression (CAT, luciferase, β-gal, GFP and the like), e.g., via chemiluminescence, fluorescence, colorimetric reactions,

15   antibody binding, inducible markers, etc.

"Inhibitors," "activators," and "modulators" of angiogenesis and tumorigenesis polynucleotide and polypeptide sequences are used to refer to activating, inhibitory, or modulating molecules identified using *in vitro* and *in vivo* assays of angiogenesis and tumorigenesis polynucleotide and polypeptide sequences. Inhibitors are

20   compounds that, e.g., bind to, partially or totally block activity, decrease, prevent, delay activation, inactivate, desensitize, or down regulate the activity or expression of angiogenesis and tumorigenesis proteins, e.g., antagonists. "Activators" are compounds that increase, open, activate, facilitate, enhance activation, sensitize, agonize, or up regulate angiogenesis and tumorigenesis protein activity, agonists. Inhibitors, activators,

25   or modulators also include genetically modified versions of angiogenesis and tumorigenesis proteins, e.g., versions with altered activity, as well as naturally occurring and synthetic ligands, antagonists, agonists, antibodies, peptides, cyclic peptides, nucleic acids, antisense molecules, ribozymes, RNAi molecules, small organic molecules and the like. Such assays for inhibitors and activators include, e.g., expressing angiogenesis or

30   tumorigenesis protein *in vitro*, in cells, or cell extracts, applying putative modulator compounds, and then determining the functional effects on activity, as described above.

Samples or assays comprising angiogenesis or tumorigenesis proteins that are treated with a potential activator, inhibitor, or modulator are compared to control samples without the inhibitor, activator, or modulator to examine the extent of inhibition.

Control samples (untreated with inhibitors) are assigned a relative protein activity value of 100%. Inhibition of an angiogenesis or tumorigenesis protein is achieved when the activity value relative to the control is about 80%, preferably 50%, more preferably 25-0%. Activation of an angiogenesis or tumorigenesis protein is achieved when the activity value relative to the control (untreated with activators) is 110%, more preferably 150%, more preferably 200-500% (i.e., two to five fold higher relative to the control), more preferably 1000-3000% higher.

The term "test compound" or "drug candidate" or "modulator" or grammatical equivalents as used herein describes any molecule, either naturally occurring or synthetic, e.g., protein, oligopeptide (e.g., from about 5 to about 25 amino acids in length, preferably from about 10 to 20 or 12 to 18 amino acids in length, preferably 12, 15, or 18 amino acids in length), small organic molecule, polysaccharide, peptide, circular peptide, lipid, fatty acid, siRNA, polynucleotide, oligonucleotide, etc., to be tested for the capacity to directly or indirectly modulate angiogenesis and tumorigenesis. The test compound can be in the form of a library of test compounds, such a combinatorial or randomized library that provides a sufficient range of diversity. Test compounds are optionally linked to a fusion partner, e.g., targeting compounds, rescue compounds, dimerization compounds, stabilizing compounds, addressable compounds, and other functional moieties. Conventionally, new chemical entities with useful properties are generated by identifying a test compound (called a "lead compound") with some desirable property or activity, e.g., inhibiting activity, creating variants of the lead compound, and evaluating the property and activity of those variant compounds. Often, high throughput screening (HTS) methods are employed for such an analysis.

A "small organic molecule" refers to an organic molecule, either naturally occurring or synthetic, that has a molecular weight of more than about 50 daltons and less than about 2500 daltons, preferably less than about 2000 daltons, preferably between about 100 to about 1000 daltons, more preferably between about 200 to about 500 daltons.

"RNAi molecule" or an "siRNA" refers to a nucleic acid that forms a double stranded RNA, which double stranded RNA has the ability to reduce or inhibit expression of a gene or target gene when the siRNA expressed in the same cell as the gene or target gene. "siRNA" thus refers to the double stranded RNA formed by the complementary strands. The complementary portions of the siRNA that hybridize to form the double stranded molecule typically have substantial or complete identity. In one

embodiment, an siRNA refers to a nucleic acid that has substantial or complete identity to a target gene and forms a double stranded siRNA. The sequence of the siRNA can correspond to the full length target gene, or a subsequence thereof. Typically, the siRNA is at least about 15-50 nucleotides in length (e.g., each complementary sequence of the double stranded siRNA is 15-50 nucleotides in length, and the double stranded siRNA is about 15-50 base pairs in length, preferable about preferably about 20-30 base nucleotides, preferably about 20-25 nucleotides in length, e.g., 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30 nucleotides in length.

"Biological sample" include sections of tissues such as biopsy and autopsy samples, and frozen sections taken for histologic purposes. Such samples include blood, sputum, tissue, cultured cells, e.g., primary cultures, explants, and transformed cells, stool, urine, etc. A biological sample is typically obtained from a eukaryotic organism, most preferably a mammal such as a primate, e.g., chimpanzee or human; cow; dog; cat; a rodent, e.g., guinea pig, rat, mouse; rabbit; or a bird; reptile; or fish.

The terms "identical" or percent "identity," in the context of two or more nucleic acids or polypeptide sequences, refer to two or more sequences or subsequences that are the same or have a specified percentage of amino acid residues or nucleotides that are the same (i.e., about 70% identity, preferably 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or higher identity over a specified region (e.g., SEQ ID NO:1 or 2), when compared and aligned for maximum correspondence over a comparison window or designated region) as measured using a BLAST or BLAST 2.0 sequence comparison algorithms with default parameters described below, or by manual alignment and visual inspection (*see, e.g.*, NCBI web site or the like). Such sequences are then said to be "substantially identical." This definition also refers to, or may be applied to, the compliment of a test sequence. The definition also includes sequences that have deletions and/or additions, as well as those that have substitutions. As described below, the preferred algorithms can account for gaps and the like. Preferably, identity exists over a region that is at least about 25 amino acids or nucleotides in length, or more preferably over a region that is 50-100 amino acids or nucleotides in length.

For sequence comparison, typically one sequence acts as a reference sequence, to which test sequences are compared. When using a sequence comparison algorithm, test and reference sequences are entered into a computer, subsequence coordinates are designated, if necessary, and sequence algorithm program parameters are designated. Preferably, default program parameters can be used, or alternative parameters

can be designated. The sequence comparison algorithm then calculates the percent sequence identities for the test sequences relative to the reference sequence, based on the program parameters.

A "comparison window", as used herein, includes reference to a segment

5   of any one of the number of contiguous positions selected from the group consisting of from 20 to 600, usually about 50 to about 200, more usually about 100 to about 150 in which a sequence may be compared to a reference sequence of the same number of contiguous positions after the two sequences are optimally aligned. Methods of alignment of sequences for comparison are well-known in the art. Optimal alignment of

10   sequences for comparison can be conducted, e.g., by the local homology algorithm of Smith & Waterman, *Adv. Appl. Math.* 2:482 (1981), by the homology alignment algorithm of Needleman & Wunsch, *J. Mol. Biol.* 48:443 (1970), by the search for similarity method of Pearson & Lipman, *Proc. Nat'l. Acad. Sci. USA* 85:2444 (1988), by computerized implementations of these algorithms (GAP, BESTFIT, FASTA, and

15   TFASTA in the Wisconsin Genetics Software Package, Genetics Computer Group, 575 , Science Dr., Madison, WI), or by manual alignment and visual inspection (*see, e.g., Current Protocols in Molecular Biology* (Ausubel *et al.*, eds. 1995 supplement)).

A preferred example of algorithm that is suitable for determining percent sequence identity and sequence similarity are the BLAST and BLAST 2.0 algorithms,

20   which are described in Altschul *et al., Nuc. Acids Res.* 25:3389-3402 (1977) and Altschul *et al., J. Mol. Biol.* 215:403-410 (1990), respectively. BLAST and BLAST 2.0 are used, with the parameters described herein, to determine percent sequence identity for the nucleic acids and proteins of the invention. Software for performing BLAST analyses is publicly available through the National Center for Biotechnology Information. This

25   algorithm involves first identifying high scoring sequence pairs (HSPs) by identifying short words of length W in the query sequence, which either match or satisfy some positive-valued threshold score T when aligned with a word of the same length in a database sequence. T is referred to as the neighborhood word score threshold (Altschul *et al., supra*). These initial neighborhood word hits act as seeds for initiating searches to

30   find longer HSPs containing them. The word hits are extended in both directions along each sequence for as far as the cumulative alignment score can be increased. Cumulative scores are calculated using, for nucleotide sequences, the parameters M (reward score for a pair of matching residues; always > 0) and N (penalty score for mismatching residues; always < 0). For amino acid sequences, a scoring matrix is used to calculate the

cumulative score. Extension of the word hits in each direction are halted when: the cumulative alignment score falls off by the quantity X from its maximum achieved value; the cumulative score goes to zero or below, due to the accumulation of one or more negative-scoring residue alignments; or the end of either sequence is reached. The

5   BLAST algorithm parameters W, T, and X determine the sensitivity and speed of the alignment. The BLASTN program (for nucleotide sequences) uses as defaults a wordlength (W) of 11, an expectation (E) of 10, M=5, N=-4 and a comparison of both strands. For amino acid sequences, the BLASTP program uses as defaults a wordlength of 3, and expectation (E) of 10, and the BLOSUM62 scoring matrix (*see* Henikoff &

10   Henikoff, *Proc. Natl. Acad. Sci. USA* 89:10915 (1989)) alignments (B) of 50, expectation (E) of 10, M=5, N=-4, and a comparison of both strands.

"Nucleic acid" refers to deoxyribonucleotides or ribonucleotides and polymers thereof in single- or double-stranded form. The term encompasses nucleic acids containing known nucleotide analogs or modified backbone residues or linkages, which

15   are synthetic, naturally occurring, and non-naturally occurring, which have similar binding properties as the reference nucleic acid, and which are metabolized in a manner similar to the reference nucleotides. Examples of such analogs include, without limitation, phosphorothioates, phosphoramidates, methyl phosphonates, chiral-methyl phosphonates, 2-O-methyl ribonucleotides, peptide-nucleic acids (PNAs).

20   Unless otherwise indicated, a particular nucleic acid sequence also implicitly encompasses conservatively modified variants thereof (e.g., degenerate codon substitutions) and complementary sequences, as well as the sequence explicitly indicated. Specifically, degenerate codon substitutions may be achieved by generating sequences in which the third position of one or more selected (or all) codons is substituted with mixed-

25   base and/or deoxyinosine residues (Batzer *et al., Nucleic Acid Res.* 19:5081 (1991); Ohtsuka *et al., J. Biol. Chem.* 260:2605-2608 (1985); Rossolini *et al., Mol. Cell. Probes* 8:91-98 (1994)). The term nucleic acid is used interchangeably with gene, cDNA, mRNA, oligonucleotide, and polynucleotide.

A particular nucleic acid sequence also implicitly encompasses "splice

30   variants." Similarly, a particular protein encoded by a nucleic acid implicitly encompasses any protein encoded by a splice variant of that nucleic acid. "Splice variants," as the name suggests, are products of alternative splicing of a gene. After transcription, an initial nucleic acid transcript may be spliced such that different (alternate) nucleic acid splice products encode different polypeptides. Mechanisms for

the production of splice variants vary, but include alternate splicing of exons. Alternate polypeptides derived from the same nucleic acid by read-through transcription are also encompassed by this definition. Any products of a splicing reaction, including recombinant forms of the splice products, are included in this definition.

5   The terms "polypeptide," "peptide" and "protein" are used interchangeably herein to refer to a polymer of amino acid residues. The terms apply to amino acid polymers in which one or more amino acid residue is an artificial chemical mimetic of a corresponding naturally occurring amino acid, as well as to naturally occurring amino acid polymers and non-naturally occurring amino acid polymer.

10   The term "amino acid" refers to naturally occurring and synthetic amino acids, as well as amino acid analogs and amino acid mimetics that function in a manner similar to the naturally occurring amino acids. Naturally occurring amino acids are those encoded by the genetic code, as well as those amino acids that are later modified, e.g., hydroxyproline, γ-carboxyglutamate, and O-phosphoserine. Amino acid analogs refers to
15   compounds that have the same basic chemical structure as a naturally occurring amino acid, i.e., an α carbon that is bound to a hydrogen, a carboxyl group, an amino group, and an R group, e.g., homoserine, norleucine, methionine sulfoxide, methionine methyl sulfonium. Such analogs have modified R groups (e.g., norleucine) or modified peptide backbones, but retain the same basic chemical structure as a naturally occurring amino
20   acid. Amino acid mimetics refers to chemical compounds that have a structure that is different from the general chemical structure of an amino acid, but that functions in a manner similar to a naturally occurring amino acid.

Amino acids may be referred to herein by either their commonly known three letter symbols or by the one-letter symbols recommended by the IUPAC-IUB
25   Biochemical Nomenclature Commission. Nucleotides, likewise, may be referred to by their commonly accepted single-letter codes.

"Conservatively modified variants" applies to both amino acid and nucleic acid sequences. With respect to particular nucleic acid sequences, conservatively modified variants refers to those nucleic acids which encode identical or essentially
30   identical amino acid sequences, or where the nucleic acid does not encode an amino acid sequence, to essentially identical sequences. Because of the degeneracy of the genetic code, a large number of functionally identical nucleic acids encode any given protein. For instance, the codons GCA, GCC, GCG and GCU all encode the amino acid alanine. Thus, at every position where an alanine is specified by a codon, the codon can be altered

to any of the corresponding codons described without altering the encoded polypeptide. Such nucleic acid variations are "silent variations," which are one species of conservatively modified variations. Every nucleic acid sequence herein which encodes a polypeptide also describes every possible silent variation of the nucleic acid. One of skill will recognize that each codon in a nucleic acid (except AUG, which is ordinarily the only codon for methionine, and TGG, which is ordinarily the only codon for tryptophan) can be modified to yield a functionally identical molecule. Accordingly, each silent variation of a nucleic acid which encodes a polypeptide is implicit in each described sequence with respect to the expression product, but not with respect to actual probe sequences.

As to amino acid sequences, one of skill will recognize that individual substitutions, deletions or additions to a nucleic acid, peptide, polypeptide, or protein sequence which alters, adds or deletes a single amino acid or a small percentage of amino acids in the encoded sequence is a "conservatively modified variant" where the alteration results in the substitution of an amino acid with a chemically similar amino acid. Conservative substitution tables providing functionally similar amino acids are well known in the art. Such conservatively modified variants are in addition to and do not exclude polymorphic variants, interspecies homologs, and alleles of the invention.

The following eight groups each contain amino acids that are conservative substitutions for one another: 1) Alanine (A), Glycine (G); 2) Aspartic acid (D), Glutamic acid (E); 3) Asparagine (N), Glutamine (Q); 4) Arginine (R), Lysine (K); 5) Isoleucine (I), Leucine (L), Methionine (M), Valine (V); 6) Phenylalanine (F), Tyrosine (Y), Tryptophan (W); 7) Serine (S), Threonine (T); and 8) Cysteine (C), Methionine (M) (*see, e.g.*, Creighton, *Proteins* (1984)).

Macromolecular structures such as polypeptide structures can be described in terms of various levels of organization. For a general discussion of this organization, *see, e.g.*, Alberts *et al.*, *Molecular Biology of the Cell* (3rd ed., 1994) and Cantor and Schimmel, *Biophysical Chemistry Part I: The Conformation of Biological Macromolecules* (1980). "Primary structure" refers to the amino acid sequence of a particular peptide. "Secondary structure" refers to locally ordered, three dimensional structures within a polypeptide. These structures are commonly known as domains, e.g., transmembrane domains, pore domains, and cytoplasmic tail domains. Domains are portions of a polypeptide that form a compact unit of the polypeptide and are typically 15 to 350 amino acids long. Exemplary domains include domains with enzymatic activity,

e.g., ligand binding domains, etc. Typical domains are made up of sections of lesser organization such as stretches of β-sheet and α-helices. "Tertiary structure" refers to the complete three dimensional structure of a polypeptide monomer. "Quaternary structure" refers to the three dimensional structure formed by the noncovalent association of

5   independent tertiary units. Anisotropic terms are also known as energy terms.

A "label" or a "detectable moiety" is a composition detectable by spectroscopic, photochemical, biochemical, immunochemical, chemical, or other physical means. For example, useful labels include ^{32}P, fluorescent dyes, electron-dense reagents, enzymes (e.g., as commonly used in an ELISA), biotin, digoxigenin, or haptens and

10   proteins which can be made detectable, e.g., by incorporating a radiolabel into the peptide or used to detect antibodies specifically reactive with the peptide.

The term "recombinant" when used with reference, e.g., to a cell, or nucleic acid, protein, or vector, indicates that the cell, nucleic acid, protein or vector, has been modified by the introduction of a heterologous nucleic acid or protein or the

15   alteration of a native nucleic acid or protein, or that the cell is derived from a cell so modified. Thus, for example, recombinant cells express genes that are not found within the native (non-recombinant) form of the cell or express native genes that are otherwise abnormally expressed, under expressed or not expressed at all.

The term "heterologous" when used with reference to portions of a nucleic

20   acid indicates that the nucleic acid comprises two or more subsequences that are not found in the same relationship to each other in nature. For instance, the nucleic acid is typically recombinantly produced, having two or more sequences from unrelated genes arranged to make a new functional nucleic acid, e.g., a promoter from one source and a coding region from another source. Similarly, a heterologous protein indicates that the

25   protein comprises two or more subsequences that are not found in the same relationship to each other in nature (e.g., a fusion protein).

The phrase "stringent hybridization conditions" refers to conditions under which a probe will hybridize to its target subsequence, typically in a complex mixture of nucleic acids, but to no other sequences. Stringent conditions are sequence-dependent

30   and will be different in different circumstances. Longer sequences hybridize specifically at higher temperatures. An extensive guide to the hybridization of nucleic acids is found in Tijssen, *Techniques in Biochemistry and Molecular Biology--Hybridization with Nucleic Probes*, "Overview of principles of hybridization and the strategy of nucleic acid assays" (1993). Generally, stringent conditions are selected to be about 5-10°C lower

than the thermal melting point (T_m) for the specific sequence at a defined ionic strength pH. The T_m is the temperature (under defined ionic strength, pH, and nucleic concentration) at which 50% of the probes complementary to the target hybridize to the target sequence at equilibrium (as the target sequences are present in excess, at T_m, 50%

5   of the probes are occupied at equilibrium). Stringent conditions may also be achieved with the addition of destabilizing agents such as formamide. For selective or specific hybridization, a positive signal is at least two times background, preferably 10 times background hybridization. Exemplary stringent hybridization conditions can be as following: 50% formamide, 5x SSC, and 1% SDS, incubating at 42°C, or, 5x SSC, 1%

10   SDS, incubating at 65°C, with wash in 0.2x SSC, and 0.1% SDS at 65°C.

Nucleic acids that do not hybridize to each other under stringent conditions are still substantially identical if the polypeptides which they encode are substantially identical. This occurs, for example, when a copy of a nucleic acid is created using the maximum codon degeneracy permitted by the genetic code. In such cases, the nucleic

15   acids typically hybridize under moderately stringent hybridization conditions. Exemplary "moderately stringent hybridization conditions" include a hybridization in a buffer of 40% formamide, 1 M NaCl, 1% SDS at 37°C, and a wash in 1X SSC at 45°C. A positive hybridization is at least twice background. Those of ordinary skill will readily recognize that alternative hybridization and wash conditions can be utilized to provide conditions of

20   similar stringency. Additional guidelines for determining hybridization parameters are provided in numerous reference, e.g., and *Current Protocols in Molecular Biology*, ed. Ausubel, *et al.*

For PCR, a temperature of about 36°C is typical for low stringency amplification, although annealing temperatures may vary between about 32°C and 48°C

25   depending on primer length. For high stringency PCR amplification, a temperature of about 62°C is typical, although high stringency annealing temperatures can range from about 50°C to about 65°C, depending on the primer length and specificity. Typical cycle conditions for both high and low stringency amplifications include a denaturation phase of 90°C - 95°C for 30 sec - 2 min., an annealing phase lasting 30 sec. - 2 min., and an

30   extension phase of about 72°C for 1 - 2 min. Protocols and guidelines for low and high stringency amplification reactions are provided, e.g., in Innis *et al.* (1990) *PCR Protocols, A Guide to Methods and Applications*, Academic Press, Inc. N.Y.).

"Antibody" refers to a polypeptide comprising a framework region from an immunoglobulin gene or fragments thereof that specifically binds and recognizes an antigen. The recognized immunoglobulin genes include the kappa, lambda, alpha, gamma, delta, epsilon, and mu constant region genes, as well as the myriad

5 immunoglobulin variable region genes. Light chains are classified as either kappa or lambda. Heavy chains are classified as gamma, mu, alpha, delta, or epsilon, which in turn define the immunoglobulin classes, IgG, IgM, IgA, IgD and IgE, respectively. Typically, the antigen-binding region of an antibody will be most critical in specificity and affinity of binding.

10 An exemplary immunoglobulin (antibody) structural unit comprises a tetramer. Each tetramer is composed of two identical pairs of polypeptide chains, each pair having one "light" (about 25 kD) and one "heavy" chain (about 50-70 kD). The N-terminus of each chain defines a variable region of about 100 to 110 or more amino acids primarily responsible for antigen recognition. The terms variable light chain (V_L) and

15 variable heavy chain (V_H) refer to these light and heavy chains respectively.

Antibodies exist, e.g., as intact immunoglobulins or as a number of well-characterized fragments produced by digestion with various peptidases. Thus, for example, pepsin digests an antibody below the disulfide linkages in the hinge region to produce F(ab)'$_2$, a dimer of Fab which itself is a light chain joined to V_H-C_H1 by a

20 disulfide bond. The F(ab)'$_2$ may be reduced under mild conditions to break the disulfide linkage in the hinge region, thereby converting the F(ab)'$_2$ dimer into an Fab' monomer. The Fab' monomer is essentially Fab with part of the hinge region (*see Fundamental Immunology* (Paul ed., 3d ed. 1993). While various antibody fragments are defined in terms of the digestion of an intact antibody, one of skill will appreciate that such

25 fragments may be synthesized *de novo* either chemically or by using recombinant DNA methodology. Thus, the term antibody, as used herein, also includes antibody fragments either produced by the modification of whole antibodies, or those synthesized *de novo* using recombinant DNA methodologies (e.g., single chain Fv) or those identified using phage display libraries (*see, e.g.*, McCafferty *et al.*, *Nature* 348:552-554 (1990))

30 For preparation of antibodies, e.g., recombinant, monoclonal, or polyclonal antibodies, many technique known in the art can be used (*see, e.g.*, Kohler & Milstein, *Nature* 256:495-497 (1975); Kozbor *et al.*, *Immunology Today* 4: 72 (1983); Cole *et al.*, pp. 77-96 in *Monoclonal Antibodies and Cancer Therapy*, Alan R. Liss, Inc. (1985); Coligan, *Current Protocols in Immunology* (1991); Harlow & Lane, *Antibodies, A*

Laboratory Manual (1988); and Goding, *Monoclonal Antibodies: Principles and Practice* (2d ed. 1986)). The genes encoding the heavy and light chains of an antibody of interest can be cloned from a cell, e.g., the genes encoding a monoclonal antibody can be cloned from a hybridoma and used to produce a recombinant monoclonal antibody. Gene

5   libraries encoding heavy and light chains of monoclonal antibodies can also be made from hybridoma or plasma cells. Random combinations of the heavy and light chain gene products generate a large pool of antibodies with different antigenic specificity (*see, e.g.,* Kuby, *Immunology* (3rd ed. 1997)). Techniques for the production of single chain antibodies or recombinant antibodies (U.S. Patent 4,946,778, U.S. Patent No. 4,816,567)

10   can be adapted to produce antibodies to polypeptides of this invention. Also, transgenic mice, or other organisms such as other mammals, may be used to express humanized or human antibodies (*see, e.g.,* U.S. Patent Nos. 5,545,807; 5,545,806; 5,569,825; 5,625,126; 5,633,425; 5,661,016, Marks *et al., Bio/Technology* 10:779-783 (1992); Lonberg *et al., Nature* 368:856-859 (1994); Morrison, *Nature* 368:812-13 (1994);

15   Fishwild *et al., Nature Biotechnology* 14:845-51 (1996); Neuberger, *Nature Biotechnology* 14:826 (1996); and Lonberg & Huszar, *Intern. Rev. Immunol.* 13:65-93 (1995)). Alternatively, phage display technology can be used to identify antibodies and heteromeric Fab fragments that specifically bind to selected antigens (*see, e.g.,* McCafferty *et al., Nature* 348:552-554 (1990); Marks *et al., Biotechnology* 10:779-783

20   (1992)). Antibodies can also be made bispecific, i.e., able to recognize two different antigens (*see, e.g.,* WO 93/08829, Traunecker *et al., EMBO J.* 10:3655-3659 (1991); and Suresh *et al., Methods in Enzymology* 121:210 (1986)). Antibodies can also be heteroconjugates, e.g., two covalently joined antibodies, or immunotoxins (*see, e.g.,* U.S. Patent No. 4,676,980 , WO 91/00360; WO 92/200373; and EP 03089).

25   Methods for humanizing or primatizing non-human antibodies are well known in the art. Generally, a humanized antibody has one or more amino acid residues introduced into it from a source which is non-human. These non-human amino acid residues are often referred to as import residues, which are typically taken from an import variable domain. Humanization can be essentially performed following the method of

30   Winter and co-workers (*see, e.g.,* Jones *et al., Nature* 321:522-525 (1986); Riechmann *et al., Nature* 332:323-327 (1988); Verhoeyen *et al., Science* 239:1534-1536 (1988) and Presta, *Curr. Op. Struct. Biol.* 2:593-596 (1992)), by substituting rodent CDRs or CDR sequences for the corresponding sequences of a human antibody. Accordingly, such humanized antibodies are chimeric antibodies (U.S. Patent No. 4,816,567), wherein

substantially less than an intact human variable domain has been substituted by the corresponding sequence from a non-human species. In practice, humanized antibodies are typically human antibodies in which some CDR residues and possibly some FR residues are substituted by residues from analogous sites in rodent antibodies.

5   A "chimeric antibody" is an antibody molecule in which (a) the constant region, or a portion thereof, is altered, replaced or exchanged so that the antigen binding site (variable region) is linked to a constant region of a different or altered class, effector function and/or species, or an entirely different molecule which confers new properties to the chimeric antibody, e.g., an enzyme, toxin, hormone, growth factor, drug, etc.; or (b)

10   the variable region, or a portion thereof, is altered, replaced or exchanged with a variable region having a different or altered antigen specificity.

In one embodiment, the antibody is conjugated to an "effector" moiety. The effector moiety can be any number of molecules, including labeling moieties such as radioactive labels or fluorescent labels, or can be a therapeutic moiety. In one aspect the

15   antibody modulates the activity of the protein.

The phrase "specifically (or selectively) binds" to an antibody or "specifically (or selectively) immunoreactive with," when referring to a protein or peptide, refers to a binding reaction that is determinative of the presence of the protein, often in a heterogeneous population of proteins and other biologics. Thus, under

20   designated immunoassay conditions, the specified antibodies bind to a particular protein at least two times the background and more typically more than 10 to 100 times background. Specific binding to an antibody under such conditions requires an antibody that is selected for its specificity for a particular protein. For example, polyclonal antibodies, polymorphic variants, alleles, orthologs, and conservatively modified variants,

25   or splice variants, or portions thereof, can be selected to obtain only those polyclonal antibodies that are specifically immunoreactive with angiogenesis proteins and not with other proteins. This selection may be achieved by subtracting out antibodies that cross-react with other molecules. A variety of immunoassay formats may be used to select antibodies specifically immunoreactive with a particular protein. For example, solid-

30   phase ELISA immunoassays are routinely used to select antibodies specifically immunoreactive with a protein (*see, e.g.*, Harlow & Lane, *Antibodies, A Laboratory Manual* (1988) for a description of immunoassay formats and conditions that can be used to determine specific immunoreactivity).

Assays for proteins that modulate angiogenesis, tumorigenesis, and cellular proliferation

High throughput functional genomics assays can be used to identify modulators of angiogenesis and tumorigenesis. Such assays can monitor changes in cell surface marker expression, $\alpha v \beta 3$ integrin production, proliferation, and differentiation using either cell lines or primary cells. Typically, early passage or primary endothelial cells are contacted with a cDNA or a random peptide library (encoded by nucleic acids). The cDNA library can comprise sense, antisense, full length, and truncated cDNAs. The peptide library is encoded by nucleic acids. The effect of the cDNA or peptide library on the endothelial cells is then monitored, using an assay such as cell surface marker expression (e.g., $\alpha v \beta 3$ integrin) or a phenotypic assay for angiogenesis such as migration towards an ECM (extracellular matrix) component (*see, e.g.*, Klemke *et al.*, *J. Cell Biol.* 4:961-972 (1998)) or endothelial cell tube formation assays, as well as other bioassays such as the chick CAM assay, the mouse corneal assay, haptotaxis assays, VEGF-R assays, co-culture tube formation assays, and assays measuring the effect of administering potential modulators on implanted tumors. The effect of the cDNA or peptide can be validated and distinguished from somatic mutations, using, e.g., regulatable expression of the nucleic acid such as expression from a tetracycline promoter. cDNAs and nucleic acids encoding peptides can be rescued using techniques known to those of skill in the art, e.g., using a sequence tags. *In vivo* assays for tumor growth, such as mouse xenograft models, can also be used.

Proteins interacting with the peptide or with the protein encoded by the cDNA can be isolated using a yeast two-hybrid system, mammalian two hybrid system, or phage display screen, etc. Targets so identified can be further used as bait in these assays to identify additional members of the angiogenesis pathway, which members are also targets for drug development (*see, e.g.*, Fields *et al.*, *Nature* 340:245 (1989); Vasavada *et al.*, *Proc. Nat'l Acad. Sci. USA* 88:10686 (1991); Fearon *et al.*, *Proc. Nat'l Acad. Sci. USA* 89:7958 (1992); Dang *et al.*, *Mol. Cell. Biol.* 11:954 (1991); Chien *et al.*, *Proc. Nat'l Acad. Sci. USA* 9578 (1991); and U.S. Patent Nos. 5,283,173, 5,667,973, 5,468,614, 5,525,490, and 5,637,463).

Suitable endothelial cell lines include human umbilical vein cells (*see, e.g.*, Jaffe *et al.*, *J. Clin. Invest.* 52:2745-2754 (1973)); human adult dermal capillary-derived cells (*see, e.g.*, Davison *et al.*, *In Vitro* 19:937-945 (1983)); human adipose capillary derived cells (*see, e.g.*, Kern *et al.*, *J. Clin Invest.* 71:1822-1829 (1983); bovine aorta (*see,*

e.g., Booyse *et al., Thromb. Diathes. Ahemorrh.* 34:825-839 (1975); and rat brain capillary derived cells (*see, e.g.*, Bowman *et al., In Vitro* 17:353-362 (1981)). For culture of endothelial cell lines, explants, and primary cells, *see* Freshney *et al., Culture of Animal Cells* (3rd ed. 1994). Suitable angiogenesis cell surface markers include

5 alphavbeta3 integrin (*see, e.g.*, Elicerir & Cheresh, *Cancer J. Sci. Am.* 6 Supp. 3:S245-249 (2000), Maeshima *et al., J. Biol. Chem.* (June 8, 2001)).

Cell surface markers such as αvβ3 can be assayed using fluorescently labeled antibodies and FACS. Cell proliferation can be measured using ^{3}H-thymidine or dye inclusion. Angiogenesis or tumorigenesis phenotype is measured by loss of

10 phenotype observation.

cDNA libraries are made from any suitable source, preferably from endothelial cells. Libraries encoding random peptides are made according to techniques well known to those of skill in the art (*see, e.g.*, U.S. Patent No. 6,153,380, 6,114,111, and 6,180,343). Any suitable vector can be used for the cDNA and peptide libraries,

15 including, e.g., retroviral vectors.

In a preferred embodiment, target proteins that modulate angiogenesis or tumorigenesis are identified using a high throughput cell based assay (using a microtiter plate format) and FACS screening for αvβ3 cell surface expression. cDNA libraries are made which include, e.g., sense, antisense, full length, and truncated cDNAs. The

20 cDNAs are cloned into a retroviral vector. Endothelial cells are infected with the library, cultured for a short effector phase and then the cells with reduced αvβ3 surface levels are enriched by antibody staining and magnetic cell sorting. The enriched cell population is then sorted into microtiter plates using fluorescent antibodies and FACS. Resultant cell colonies are analyzed by immunofluorescence for reduced αvβ3 surface levels. Selected

25 colonies are infected with wild type MMLV virus to rescue the proviral vector. The infectious supernatant is used to infect endothelial cells, which are subsequently analyzed for αvβ3 levels by FACS. The cDNA is isolated and sequenced to determined if it represents a wild type or mutated cDNA, e.g., whether the cDNA represents a negative transdominant mutant. Optionally, a marker such as GFP can be used to select for

30 retrovirally infected cells.

Isolation of nucleic acids

This invention relies on routine techniques in the field of recombinant genetics. Basic texts disclosing the general methods of use in this invention include

Sambrook *et al.*, *Molecular Cloning, A Laboratory Manual* (2nd ed. 1989); Kriegler, *Gene Transfer and Expression: A Laboratory Manual* (1990); and *Current Protocols in Molecular Biology* (Ausubel *et al.*, eds., 1994)).

Nucleic acids, polymorphic variants, orthologs, and alleles can be isolated using nucleic acid probes and oligonucleotides under stringent hybridization conditions, by screening libraries. Alternatively, expression libraries can be used to clone angiogenesis proteins, polymorphic variants, orthologs, and alleles by detecting expressed homologs immunologically with antisera or purified antibodies made against human angiogenesis proteins or portions thereof.

To make a cDNA library, one should choose a source that is rich in the desired RNA, e.g., endothelial cells. The mRNA is then made into cDNA using reverse transcriptase, ligated into a recombinant vector, and transfected into a recombinant host for propagation, screening and cloning. Methods for making and screening cDNA libraries are well known (*see, e.g.,* Gubler & Hoffman, *Gene* 25:263-269 (1983); Sambrook *et al., supra*; Ausubel *et al., supra*).

For a genomic library, the DNA is extracted from the tissue and either mechanically sheared or enzymatically digested to yield fragments of about 12-20 kb. The fragments are then separated by gradient centrifugation from undesired sizes and are constructed in bacteriophage lambda vectors. These vectors and phage are packaged *in vitro*. Recombinant phage are analyzed by plaque hybridization as described in Benton & Davis, *Science* 196:180-182 (1977). Colony hybridization is carried out as generally described in Grunstein *et al., Proc. Natl. Acad. Sci. USA.,* 72:3961-3965 (1975).

An alternative method of isolating nucleic acids and orthologs, alleles, mutants, polymorphic variants, and conservatively modified variants combines the use of synthetic oligonucleotide primers and amplification of an RNA or DNA template (*see* U.S. Patents 4,683,195 and 4,683,202; *PCR Protocols: A Guide to Methods and Applications* (Innis *et al.*, eds, 1990)). Methods such as polymerase chain reaction (PCR) and ligase chain reaction (LCR) can be used to amplify nucleic acid sequences directly from mRNA, from cDNA, from genomic libraries or cDNA libraries. Degenerate oligonucleotides can be designed to amplify homologs using the sequences provided herein. Restriction endonuclease sites can be incorporated into the primers. Polymerase chain reaction or other *in vitro* amplification methods may also be useful, for example, to clone nucleic acid sequences that code for proteins to be expressed, to make nucleic acids to use as probes for detecting the presence of angiogenesis protein encoding mRNA in

physiological samples, for nucleic acid sequencing, or for other purposes. Genes amplified by the PCR reaction can be purified from agarose gels and cloned into an appropriate vector.

5   Gene expression can also be analyzed by techniques known in the art, e.g., reverse transcription and amplification of mRNA, isolation of total RNA or poly A$^+$ RNA, northern blotting, dot blotting, *in situ* hybridization, RNase protection, high density polynucleotide array technology, e.g., and the like.

Nucleic acids can be used with high density oligonucleotide array technology (e.g., GeneChip^{TM}) to identify angiogenesis protein, orthologs, alleles,
10   conservatively modified variants, and polymorphic variants in this invention. In the case where the homologs being identified are linked to a known disease state, they can be used with GeneChip^{TM} as a diagnostic tool in detecting the disease in a biological sample, *see, e.g.*, Gunthand *et al., AIDS Res. Hum. Retroviruses* 14: 869-876 (1998); Kozal *et al., Nat. Med.* 2:753-759 (1996); Matson *et al., Anal. Biochem.* 224:110-106 (1995); Lockhart *et*
15   *al., Nat. Biotechnol.* 14:1675-1680 (1996); Gingeras *et al., Genome Res.* 8:435-448 (1998); Hacia *et al., Nucleic Acids Res.* 26:3865-3866 (1998).

The gene is typically cloned into intermediate vectors before transformation into prokaryotic or eukaryotic cells for replication and/or expression. These intermediate vectors are typically prokaryote vectors, e.g., plasmids, or shuttle
20   vectors.

Expression in prokaryotes and eukaryotes

To obtain high level expression of a cloned gene, such as those cDNAs encoding an angiogenesis protein, one typically subclones the desired nucleic acid into an
25   expression vector that contains a strong promoter to direct transcription, a transcription/translation terminator, and if for a nucleic acid encoding a protein, a ribosome binding site for translational initiation. Suitable bacterial promoters are well known in the art and described, e.g., in Sambrook *et al.*, and Ausubel *et al, supra*. Bacterial expression systems for expressing the protein are available in, e.g., *E. coli,*
30   *Bacillus sp.,* and *Salmonella* (Palva *et al., Gene* 22:229-235 (1983); Mosbach *et al., Nature* 302:543-545 (1983). Kits for such expression systems are commercially available. Eukaryotic expression systems for mammalian cells, yeast, and insect cells are well known in the art and are also commercially available.

Selection of the promoter used to direct expression of a heterologous nucleic acid depends on the particular application. The promoter is preferably positioned about the same distance from the heterologous transcription start site as it is from the transcription start site in its natural setting. As is known in the art, however, some

5　variation in this distance can be accommodated without loss of promoter function.

In addition to the promoter, the expression vector typically contains a transcription unit or expression cassette that contains all the additional elements required for the expression of the nucleic acid in host cells. A typical expression cassette thus contains a promoter operably linked to the nucleic acid sequence and signals required for

10　efficient polyadenylation of the transcript, ribosome binding sites, and translation termination. Additional elements of the cassette may include enhancers and, if genomic DNA is used as the structural gene, introns with functional splice donor and acceptor sites.

In addition to a promoter sequence, the expression cassette should also

15　contain a transcription termination region downstream of the structural gene to provide for efficient termination. The termination region may be obtained from the same gene as the promoter sequence or may be obtained from different genes.

The particular expression vector used to transport the genetic information into the cell is not particularly critical. Any of the conventional vectors used for

20　expression in eukaryotic or prokaryotic cells may be used. Standard bacterial expression vectors include plasmids such as pBR322 based plasmids, pSKF, pET23D, and fusion expression systems such as MBP, GST, and LacZ. Epitope tags can also be added to recombinant proteins to provide convenient methods of isolation, e.g., c-myc.

Expression vectors containing regulatory elements from eukaryotic viruses

25　are typically used in eukaryotic expression vectors, e.g., SV40 vectors, papilloma virus vectors, retroviral vectors, and vectors derived from Epstein-Barr virus. Other exemplary eukaryotic vectors include pMSG, pAV009/A$^+$, pMTO10/A$^+$, pMAMneo-5, baculovirus pDSVE, and any other vector allowing expression of proteins under the direction of the CMV promoter, SV40 early promoter, SV40 later promoter, metallothionein promoter,

30　murine mammary tumor virus promoter, Rous sarcoma virus promoter, polyhedrin promoter, or other promoters shown effective for expression in eukaryotic cells.

Expression of proteins from eukaryotic vectors can be also be regulated using inducible promoters. With inducible promoters, expression levels are tied to the concentration of inducing agents, such as tetracycline or ecdysone, by the incorporation

of response elements for these agents into the promoter. Generally, high level expression is obtained from inducible promoters only in the presence of the inducing agent; basal expression levels are minimal. Inducible expression vectors are often chosen if expression of the protein of interest is detrimental to eukaryotic cells.

5   In one embodiment, the vectors of the invention have a regulatable. promoter, e.g., tet-regulated systems and the RU-486 system (*see, e.g.*, Gossen & Bujard, *Proc. Nat'l Acad. Sci. USA* 89:5547 (1992); Oligino *et al., Gene Ther.* 5:491-496 (1998); Wang *et al., Gene Ther.* 4:432-441 (1997); Neering *et al., Blood* 88:1147-1155 (1996); and Rendahl *et al., Nat. Biotechnol.* 16:757-761 (1998)). These impart small molecule

10   control on the expression of the candidate target nucleic acids. This beneficial feature can be used to determine that a desired phenotype is caused by a transfected cDNA rather than a somatic mutation.

Some expression systems have markers that provide gene amplification such as thymidine kinase and dihydrofolate reductase. Alternatively, high yield

15   expression systems not involving gene amplification are also suitable, such as using a baculovirus vector in insect cells, with a protein encoding sequence under the direction of the polyhedrin promoter or other strong baculovirus promoters.

The elements that are typically included in expression vectors also include a replicon that functions in *E. coli*, a gene encoding antibiotic resistance to permit

20   selection of bacteria that harbor recombinant plasmids, and unique restriction sites in nonessential regions of the plasmid to allow insertion of eukaryotic sequences. The particular antibiotic resistance gene chosen is not critical, any of the many resistance genes known in the art are suitable. The prokaryotic sequences are preferably chosen such that they do not interfere with the replication of the DNA in eukaryotic cells, if

25   necessary.

Standard transfection methods are used to produce bacterial, mammalian, yeast or insect cell lines that express large quantities of protein, which are then purified using standard techniques (*see, e.g.*, Colley *et al., J. Biol. Chem.* 264:17619-17622 (1989); *Guide to Protein Purification*, in *Methods in Enzymology*, vol. 182 (Deutscher,

30   ed., 1990)). Transformation of eukaryotic and prokaryotic cells are performed according to standard techniques (*see, e.g.*, Morrison, *J. Bact.* 132:349-351 (1977); Clark-Curtiss & Curtiss, *Methods in Enzymology* 101:347-362 (Wu *et al.*, eds, 1983).

Any of the well-known procedures for introducing foreign nucleotide sequences into host cells may be used. These include the use of calcium phosphate

transfection, polybrene, protoplast fusion, electroporation, biolistics, liposomes, microinjection, plasma vectors, viral vectors and any of the other well known methods for introducing cloned genomic DNA, cDNA, synthetic DNA or other foreign genetic material into a host cell (*see, e.g.,* Sambrook *et al., supra*). It is only necessary that the

5   particular genetic engineering procedure used be capable of successfully introducing at least one gene into the host cell capable of expressing the protein of choice.

After the expression vector is introduced into the cells, the transfected cells are cultured under conditions favoring expression of the protein of choice, which is recovered from the culture using standard techniques identified below.

10

Purification of polypeptides

Either naturally occurring or recombinant protein can be purified for use in functional assays. Naturally occurring protein can be purified, e.g., from human tissue. Recombinant protein can be purified from any suitable expression system.

15   The protein may be purified to substantial purity by standard techniques, including selective precipitation with such substances as ammonium sulfate; column chromatography, immunopurification methods, and others (*see, e.g.,* Scopes, *Protein Purification: Principles and Practice* (1982); U.S. Patent No. 4,673,641; Ausubel *et al., supra;* and Sambrook *et al., supra*).

20   A number of procedures can be employed when recombinant protein is being purified. For example, proteins having established molecular adhesion properties can be reversible fused to the protein. With the appropriate ligand, angiogenesis protein can be selectively adsorbed to a purification column and then freed from the column in a relatively pure form. The fused protein is then removed by enzymatic activity. Finally,

25   protein could be purified using immunoaffinity columns.

A.   *Purification of protein from recombinant bacteria*

Recombinant proteins are expressed by transformed bacteria in large amounts, typically after promoter induction; but expression can be constitutive. Promoter

30   induction with IPTG is one example of an inducible promoter system. Bacteria are grown according to standard procedures in the art. Fresh or frozen bacteria cells are used for isolation of protein.

Proteins expressed in bacteria may form insoluble aggregates ("inclusion bodies"). Several protocols are suitable for purification of protein inclusion bodies. For

example, purification of inclusion bodies typically involves the extraction, separation and/or purification of inclusion bodies by disruption of bacterial cells, e.g., by incubation in a buffer of 50 mM TRIS/HCL pH 7.5, 50 mM NaCl, 5 mM $MgCl_2$, 1 mM DTT, 0.1 mM ATP, and 1 mM PMSF. The cell suspension can be lysed using 2-3 passages

5   through a French Press, homogenized using a Polytron (Brinkman Instruments) or sonicated on ice. Alternate methods of lysing bacteria are apparent to those of skill in the art (see, e.g., Sambrook et al., supra; Ausubel et al., supra).

If necessary, the inclusion bodies are solubilized, and the lysed cell suspension is typically centrifuged to remove unwanted insoluble matter. Proteins that

10   formed the inclusion bodies may be renatured by dilution or dialysis with a compatible buffer. Suitable solvents include, but are not limited to urea (from about 4 M to about 8 M), formamide (at least about 80%, volume/volume basis), and guanidine hydrochloride (from about 4 M to about 8 M). Some solvents which are capable of solubilizing aggregate-forming proteins, for example SDS (sodium dodecyl sulfate), 70% formic acid,

15   are inappropriate for use in this procedure due to the possibility of irreversible denaturation of the proteins, accompanied by a lack of immunogenicity and/or activity. Although guanidine hydrochloride and similar agents are denaturants, this denaturation is not irreversible and renaturation may occur upon removal (by dialysis, for example) or dilution of the denaturant, allowing re-formation of immunologically and/or biologically

20   active protein. Other suitable buffers are known to those skilled in the art. Human proteins are separated from other bacterial proteins by standard separation techniques, e.g., with Ni-NTA agarose resin.

Alternatively, it is possible to purify protein from bacteria periplasm. After lysis of the bacteria, the periplasmic fraction of the bacteria can be isolated by cold

25   osmotic shock in addition to other methods known to skill in the art. To isolate recombinant proteins from the periplasm, the bacterial cells are centrifuged to form a pellet. The pellet is resuspended in a buffer containing 20% sucrose. To lyse the cells, the bacteria are centrifuged and the pellet is resuspended in ice-cold 5 mM $MgSO_4$ and kept in an ice bath for approximately 10 minutes. The cell suspension is centrifuged and

30   the supernatant decanted and saved. The recombinant proteins present in the supernatant can be separated from the host proteins by standard separation techniques well known to those of skill in the art.

B.   *Standard protein separation techniques for purifying proteins*

Solubility fractionation

Often as an initial step, particularly if the protein mixture is complex, an
initial salt fractionation can separate many of the unwanted host cell proteins (or proteins
5   derived from the cell culture media) from the recombinant protein of interest. The
preferred salt is ammonium sulfate. Ammonium sulfate precipitates proteins by
effectively reducing the amount of water in the protein mixture. Proteins then precipitate
on the basis of their solubility. The more hydrophobic a protein is, the more likely it is to
precipitate at lower ammonium sulfate concentrations. A typical protocol includes adding
10   saturated ammonium sulfate to a protein solution so that the resultant ammonium sulfate
concentration is between 20-30%. This concentration will precipitate the most
hydrophobic of proteins. The precipitate is then discarded (unless the protein of interest
is hydrophobic) and ammonium sulfate is added to the supernatant to a concentration
known to precipitate the protein of interest. The precipitate is then solubilized in buffer
15   and the excess salt removed if necessary, either through dialysis or diafiltration. Other
methods that rely on solubility of proteins, such as cold ethanol precipitation, are well
known to those of skill in the art and can be used to fractionate complex protein mixtures.

Size differential filtration

20   The molecular weight of the protein can be used to isolate it from proteins
of greater and lesser size using ultrafiltration through membranes of different pore size
(for example, Amicon or Millipore membranes). As a first step, the protein mixture is
ultrafiltered through a membrane with a pore size that has a lower molecular weight cut-
off than the molecular weight of the protein of interest. The retentate of the ultrafiltration
25   is then ultrafiltered against a membrane with a molecular cut off greater than the
molecular weight of the protein of interest. The recombinant protein will pass through
the membrane into the filtrate. The filtrate can then be chromatographed as described
below.

30   Column chromatography

The protein can also be separated from other proteins on the basis of its
size, net surface charge, hydrophobicity, and affinity for ligands. In addition, antibodies
raised against proteins can be conjugated to column matrices and the proteins
immunopurified. All of these methods are well known in the art. It will be apparent to

one of skill that chromatographic techniques can be performed at any scale and using equipment from many different manufacturers (e.g., Pharmacia Biotech).

Assays for modulators of angiogenesis or tumorigenesis proteins

5   *A.*   *Assays*

Modulation of an angiogenesis protein, and corresponding modulation of angiogenesis or tumorigenesis, can be assessed using a variety of *in vitro* and *in vivo* assays, including high throughput ligand binding and cell based assays, as described herein. Such assays can be used to test for inhibitors and activators of the angiogenesis

10   protein, and, consequently, inhibitors and activators of angiogenesis. Such modulators of the angiogenesis protein are useful for treating angiogenesis and tumorigenesis disorders. Modulators of the angiogenesis protein are tested using either recombinant or naturally occurring protein, preferably human protein.

Measurement of an angiogenic or tumorigenic or loss-of-angiogenesis or

15   tumorigenesis phenotype on the protein or cell expressing the protein, either recombinant or naturally occurring, can be performed using a variety of assays, *in vitro, in vivo,* and *ex vivo.* For example, recombinant or naturally occurring protein can be used *in vitro,* in a ligand binding or enzymatic function assay. Protein present in a cellular extract can also be used in *in vitro* assays. Cell- and animal-based *in vivo* assays can also be used to assay

20   for angiogenesis modulators. Any suitable physical, chemical, or phenotypic change that affects activity or binding can be used to assess the influence of a test compound on the polypeptide of this invention. When the functional effects are determined using intact cells or animals, one can also measure a variety of effects such as, in the case of angiogenesis associated with tumors, tumor growth, neovascularization, endothelial tube

25   formation, cell surface markers such as $\alpha v \beta 3$, hormone release, transcriptional changes to both known and uncharacterized genetic markers (e.g., northern blots), changes in cell metabolism such as cell growth or pH changes, and changes in intracellular second messengers such as cGMP. In one embodiment, measurement of $\alpha v \beta 3$ integrin cell surface expression and FACS sorting is used to identify modulators of angiogenesis.

30

                In vitro assays

Assays to identify compounds with angiogenesis or tumorigenesis modulating activity, e.g., anti-angiogenic or anti-tumorigenic activity, can be performed *in vitro,* e.g., binding assays. Purified recombinant or naturally occurring protein can be

used in the *in vitro* methods of the invention. In addition to purified protein, the recombinant or naturally occurring protein can be part of a cellular lysate. As described below, the assay can be either solid state or soluble. Preferably, the protein is bound to a solid support, either covalently or non-covalently. Often, the *in vitro* assays of the

5   invention are ligand binding or ligand affinity assays, either non-competitive or competitive. Other *in vitro* assays include measuring changes in spectroscopic (e.g., fluorescence, absorbance, refractive index), hydrodynamic (e.g., shape), chromatographic, or solubility properties for the protein.

In one embodiment, a high throughput binding assay is performed in

10   which the protein or chimera comprising a fragment thereof is contacted with a potential modulator and incubated for a suitable amount of time. In one embodiment, the potential modulator is bound to a solid support, and the protein is added. In another embodiment, the protein is bound to a solid support. A wide variety of modulators can be used, as described below, including small organic molecules, peptides, and antibodies. A wide

15   variety of assays can be used to identify angiogenesis-modulator binding, including labeled protein-protein binding assays, electrophoretic mobility shifts, immunoassays, and the like. In some cases, the binding of the candidate modulator is determined through the use of competitive binding assays, where interference with binding of a known ligand is measured in the presence of a potential modulator. Often, either the potential

20   modulator or the known ligand is labeled.

Cell-based *in vivo* assays

In another embodiment, the protein is expressed in a cell, and functional, e.g., physical and chemical or phenotypic, changes are assayed to identify angiogenesis or

25   tumorigenesis modulators, preferably anti-angiogenesis or anti-tumorigenesis compounds. Cells expressing angiogenesis proteins can also be used in binding assays or enzymatic assays. Any suitable functional effect can be measured, as described herein. For example, ligand binding, cell surface marker expression, cellular proliferation, VEGF-R assays, co-culture assays for tube formation, and cell migration assays are all suitable

30   assays to identify potential modulators using a cell based system. Suitable cells for such cell based assays include both primary endothelial cells and cell lines, as described herein. The protein can be naturally occurring or recombinant.

As described above, in one embodiment, loss-of angiogenesis or tumorigenesis phenotype is measured by contacting endothelial cells comprising an

angiogenesis target with a potential modulator. Modulation of angiogenesis or tumorigenesis is identified by screening for cell surface marker expression, e.g., $\alpha v \beta 3$ integrin expression levels, using fluorescent antibodies and FACS sorting.

In another embodiment, cellular proliferation can be measured using ^{3}H-thymidine incorporation or dye inclusion.

In another embodiment, cellular polypeptide levels are determined by measuring the level of protein or mRNA. The level of protein or proteins are measured using immunoassays such as western blotting, ELISA and the like with an antibody that selectively binds to the polypeptide or a fragment thereof. For measurement of mRNA, amplification, e.g., using PCR, LCR, or hybridization assays, e.g., northern hybridization, RNAse protection, dot blotting, are preferred. The level of protein or mRNA is detected using directly or indirectly labeled detection agents, e.g., fluorescently or radioactively labeled nucleic acids, radioactively or enzymatically labeled antibodies, and the like, as described herein.

Alternatively, protein expression can be measured using a reporter gene system. Such a system can be devised using an angiogenesis protein promoter operably linked to a reporter gene such as chloramphenicol acetyltransferase, firefly luciferase, bacterial luciferase, β-galactosidase and alkaline phosphatase. Furthermore, the protein of interest can be used as an indirect reporter via attachment to a second reporter such as red or green fluorescent protein (*see, e.g.*, Mistili & Spector, *Nature Biotechnology* 15:961-964 (1997)). The reporter construct is typically transfected into a cell. After treatment with a potential modulator, the amount of reporter gene transcription, translation, or activity is measured according to standard techniques known to those of skill in the art.

A variety of phenotypic angiogenesis or tumorigenesis assays are known to those of skill in the art. Various models have been employed to evaluate angiogenesis (e.g., Croix *et al.*, *Science* 289:1197-1202 (2000) and Kahn *et al.*, *Amer. J. Pathol.* 156:1887-1900). Assessment of angiogenesis or tumorigenesis in the presence of a potential modulator can be performed using cell-culture-based assays, e.g., endothelial cell tube formation assays and haptotaxis assays, as well as other animal based bioassays such as the chick CAM assay, the mouse corneal assay, and assays measuring the effect of administering potential modulators on implanted tumors.

For determination of cellular proliferation, any suitable functional effect can be measured, as described herein. For example, cellular morphology (e.g., cell volume, nuclear volume, cell perimeter, and nuclear perimeter), ligand binding, kinase activity, apoptosis, cell surface marker expression, cellular proliferation, GFP positivity

5 and dye dilution assays (e.g., cell tracker assays with dyes that bind to cell membranes), DNA synthesis assays (e.g., ^{3}H-thymidine and fluorescent DNA-binding dyes such as BrdU or Hoescht dye with FACS analysis), G_0/G_1 cell cycle arrest, are all suitable assays to identify potential modulators using a cell based system. Suitable cells for such cell based assays include both primary cancer or tumor cells and cell lines, as described

10 herein, e.g., A549 (lung), MCF7 (breast, p53 wild-type), H1299 (lung, p53 null), Hela (cervical), PC3 (prostate, p53 mutant), MDA-MB-231 (breast, p53 wild-type). Cancer cell lines can be p53 mutant, p53 null, or express wild type p53.

Animal models

15 A number of animal based assays for angiogenesis or tumorigenesis phenotypes are known to those of skill in the art and can be used to assay for modulators of angiogenesis. For example, the chick CAM assay is described by O'Reilly, *et al.* Cell 79: 315-328 (1994). Briefly, 3 day old chicken embryos with intact yolks are separated from the egg and placed in a petri dish. After 3 days of incubation, a methylcellulose disc

20 containing the protein to be tested is applied to the CAM of individual embryos. After about 48 hours of incubation, the embryos and CAMs are observed to determine whether endothelial growth has been inhibited.

The mouse corneal assay involves implanting a growth factor-containing pellet, along with another pellet containing the suspected endothelial growth inhibitor, in

25 the cornea of a mouse and observing the pattern of capillaries that are elaborated in the cornea.

Angiogenesis can also be measured by determining the extent of neovascularization of a tumor. For example, carcinoma cells can be subcutaneously inoculated into athymic or nude mice or SCID mice and tumor growth then monitored.

30 Immunoassays using endothelial cell-specific antibodies are typically used to stain for vascularization of tumor and the number of vessels in the tumor.

As described above, animal models of angiogenesis find use in screening for modulators of angiogenesis and tumorigenesis. Similarly, transgenic animal technology including gene knockout technology, for example as a result of homologous

recombination with an appropriate gene targeting vector, or gene overexpression, will result in the absence or increased expression of the protein. The same technology can also be applied to make knock-out cells. When desired, tissue-specific expression or knockout of the protein may be necessary. Transgenic animals generated by such

5   methods find use as animal models of angiogenesis and are additionally useful in screening for modulators of angiogenesis and tumorigenesis.

Knock-out cells and transgenic mice can be made by insertion of a marker gene or other heterologous gene into the endogenous gene site in the mouse genome via homologous recombination. Such mice can also be made by substituting the endogenous

10   gene with a mutated version of the gene, or by mutating the endogenous gene, e.g., by exposure to carcinogens.

A DNA construct is introduced into the nuclei of embryonic stem cells. Cells containing the newly engineered genetic lesion are injected into a host mouse embryo, which is re-implanted into a recipient female. Some of these embryos develop

15   into chimeric mice that possess germ cells partially derived from the mutant cell line. Therefore, by breeding the chimeric mice it is possible to obtain a new line of mice containing the introduced genetic lesion (*see, e.g.,* Capecchi *et al., Science* 244:1288 (1989)). Chimeric targeted mice can be derived according to Hogan *et al., Manipulating the Mouse Embryo: A Laboratory Manual*, Cold Spring Harbor Laboratory (1988) and

20   *Teratocarcinomas and Embryonic Stem Cells: A Practical Approach*, Robertson, ed., IRL Press, Washington, D.C., (1987).

B.   *Modulators*

The compounds tested as modulators of the angiogenesis protein can be

25   any small organic molecule, or a biological entity, such as a protein, e.g., an antibody or peptide, a sugar, a nucleic acid, e.g., an antisense oligonucleotide, RNAi molecule, or a ribozyme, or a lipid. Alternatively, modulators can be genetically altered versions of an angiogenesis protein. Typically, test compounds will be small organic molecules, peptides, lipids, and lipid analogs.

30   Essentially any chemical compound can be used as a potential modulator or ligand in the assays of the invention, although most often compounds can be dissolved in aqueous or organic (especially DMSO-based) solutions are used. The assays are designed to screen large chemical libraries by automating the assay steps and providing compounds from any convenient source to assays, which are typically run in parallel

(e.g., in microtiter formats on microtiter plates in robotic assays). It will be appreciated that there are many suppliers of chemical compounds, including Sigma (St. Louis, MO), Aldrich (St. Louis, MO), Sigma-Aldrich (St. Louis, MO), Fluka Chemika-Biochemica Analytika (Buchs Switzerland) and the like.

5   In one preferred embodiment, high throughput screening methods involve providing a combinatorial small organic molecule or peptide library containing a large number of potential therapeutic compounds (potential modulator or ligand compounds). Such "combinatorial chemical libraries" or "ligand libraries" are then screened in one or more assays, as described herein, to identify those library members (particular chemical

10   species or subclasses) that display a desired characteristic activity. The compounds thus identified can serve as conventional "lead compounds" or can themselves be used as potential or actual therapeutics.

         A combinatorial chemical library is a collection of diverse chemical compounds generated by either chemical synthesis or biological synthesis, by combining

15   a number of chemical "building blocks" such as reagents. For example, a linear combinatorial chemical library such as a polypeptide library is formed by combining a set of chemical building blocks (amino acids) in every possible way for a given compound length (i.e., the number of amino acids in a polypeptide compound). Millions of chemical compounds can be synthesized through such combinatorial mixing of chemical building

20   blocks.

         Preparation and screening of combinatorial chemical libraries is well known to those of skill in the art. Such combinatorial chemical libraries include, but are not limited to, peptide libraries (see, e.g., U.S. Patent 5,010,175, Furka, *Int. J. Pept. Prot. Res.* 37:487-493 (1991) and Houghton *et al.*, *Nature* 354:84-88 (1991)). Other

25   chemistries for generating chemical diversity libraries can also be used. Such chemistries include, but are not limited to: peptoids (e.g., PCT Publication No. WO 91/19735), encoded peptides (e.g., PCT Publication No. WO 93/20242), random bio-oligomers (e.g., PCT Publication No. WO 92/00091), benzodiazepines (e.g., U.S. Pat. No. 5,288,514), diversomers such as hydantoins, benzodiazepines and dipeptides (Hobbs *et al.*, *Proc. Nat.*

30   *Acad. Sci. USA* 90:6909-6913 (1993)), vinylogous polypeptides (Hagihara *et al.*, *J. Amer. Chem. Soc.* 114:6568 (1992)), nonpeptidal peptidomimetics with glucose scaffolding (Hirschmann *et al.*, *J. Amer. Chem. Soc.* 114:9217-9218 (1992)), analogous organic syntheses of small compound libraries (Chen *et al.*, *J. Amer. Chem. Soc.* 116:2661 (1994)), oligocarbamates (Cho *et al.*, *Science* 261:1303 (1993)), and/or peptidyl

phosphonates (Campbell *et al., J. Org. Chem.* 59:658 (1994)), nucleic acid libraries (*see* Ausubel, Berger and Sambrook, all *supra*), peptide nucleic acid libraries (*see, e.g.,* U.S. Patent 5,539,083), antibody libraries (*see, e.g.,* Vaughn *et al., Nature Biotechnology*, 14(3):309-314 (1996) and PCT/US96/10287), carbohydrate libraries (*see, e.g.,* Liang *et*

5   *al., Science,* 274:1520-1522 (1996) and U.S. Patent 5,593,853), small organic molecule libraries (*see, e.g.,* benzodiazepines, Baum C&EN, Jan 18, page 33 (1993); isoprenoids, U.S. Patent 5,569,588; thiazolidinones and metathiazanones, U.S. Patent 5,549,974; pyrrolidines, U.S. Patents 5,525,735 and 5,519,134; morpholino compounds, U.S. Patent 5,506,337; benzodiazepines, 5,288,514, and the like).

10   Devices for the preparation of combinatorial libraries are commercially available (*see, e.g.,* 357 MPS, 390 MPS, Advanced Chem Tech, Louisville KY, Symphony, Rainin, Woburn, MA, 433A Applied Biosystems, Foster City, CA, 9050 Plus, Millipore, Bedford, MA). In addition, numerous combinatorial libraries are themselves commercially available (*see, e.g.,* ComGenex, Princeton, N.J., Asinex, Moscow, Ru,

15   Tripos, Inc., St. Louis, MO, ChemStar, Ltd, Moscow, RU, 3D Pharmaceuticals, Exton, PA, Martek Biosciences, Columbia, MD, etc.).

C.   *Solid State and soluble high throughput assays*

In one embodiment the invention provides soluble assays using an

20   angiogenesis protein, or a cell or tissue expressing an angiogenesis protein, either naturally occurring or recombinant. In another embodiment, the invention provides solid phase based *in vitro* assays in a high throughput format, where the angiogenesis protein is attached to a solid phase substrate. Any one of the assays described herein can be adapted for high throughput screening, e.g., ligand binding, cellular proliferation, cell

25   surface marker flux, e.g., $\alpha v\beta 3$ integrin, etc. In one preferred embodiment, the cell-based system using $\alpha v\beta 3$ integrin modulation and FACS assays is used in a high throughput format for identifying modulators of angiogenesis proteins, and therefore modulators of T cell angiogenesis.

In the high throughput assays of the invention, either soluble or solid state,

30   it is possible to screen up to several thousand different modulators or ligands in a single day. This methodology can be used for angiogenesis proteins *in vitro*, or for cell-based assays comprising an angiogenesis protein. In particular, each well of a microtiter plate can be used to run a separate assay against a selected potential modulator, or, if concentration or incubation time effects are to be observed, every 5-10 wells can test a

single modulator. Thus, a single standard microtiter plate can assay about 100 (e.g., 96) modulators. If 1536 well plates are used, then a single plate can easily assay from about 100- about 1500 different compounds. It is possible to assay many plates per day; assay screens for up to about 6,000, 20,000, 50,000, or more than 100,000 different compounds

5   are possible using the integrated systems of the invention.

          For a solid state reaction, the protein of interest or a fragment thereof, e.g., an extracellular domain, or a cell comprising the protein of interest or a fragment thereof as part of a fusion protein can be bound to the solid state component, directly or indirectly, via covalent or non covalent linkage e.g., via a tag. The tag can be any of a

10   variety of components. In general, a molecule which binds the tag (a tag binder) is fixed to a solid support, and the tagged molecule of interest is attached to the solid support by interaction of the tag and the tag binder.

          A number of tags and tag binders can be used, based upon known molecular interactions well described in the literature. For example, where a tag has a

15   natural binder, for example, biotin, protein A, or protein G, it can be used in conjunction with appropriate tag binders (avidin, streptavidin, neutravidin, the Fc region of an immunoglobulin, etc.) Antibodies to molecules with natural binders such as biotin are also widely available and appropriate tag binders; see, SIGMA Immunochemicals 1998 catalogue SIGMA, St. Louis MO).

20   Similarly, any haptenic or antigenic compound can be used in combination with an appropriate antibody to form a tag/tag binder pair. Thousands of specific antibodies are commercially available and many additional antibodies are described in the literature. For example, in one common configuration, the tag is a first antibody and the tag binder is a second antibody which recognizes the first antibody. In addition to

25   antibody-antigen interactions, receptor-ligand interactions are also appropriate as tag and tag-binder pairs. For example, agonists and antagonists of cell membrane receptors (e.g., cell receptor-ligand interactions such as transferrin, c-kit, viral receptor ligands, cytokine receptors, chemokine receptors, interleukin receptors, immunoglobulin receptors and antibodies, the cadherein family, the integrin family, the selectin family, and the like; see,

30   e.g., Pigott & Power, *The Adhesion Molecule Facts Book I* (1993). Similarly, toxins and venoms, viral epitopes, hormones (e.g., opiates, steroids, etc.), intracellular receptors (e.g. which mediate the effects of various small ligands, including steroids, thyroid hormone, retinoids and vitamin D; peptides), drugs, lectins, sugars, nucleic acids (both linear and

cyclic polymer configurations), oligosaccharides, proteins, phospholipids and antibodies can all interact with various cell receptors.

Synthetic polymers, such as polyurethanes, polyesters, polycarbonates, polyureas, polyamides, polyethyleneimines, polyarylene sulfides, polysiloxanes, polyimides, and polyacetates can also form an appropriate tag or tag binder. Many other tag/tag binder pairs are also useful in assay systems described herein, as would be apparent to one of skill upon review of this disclosure.

Common linkers such as peptides, polyethers, and the like can also serve as tags, and include polypeptide sequences, such as poly gly sequences of between about 5 and 200 amino acids. Such flexible linkers are known to persons of skill in the art. For example, poly(ethelyne glycol) linkers are available from Shearwater Polymers, Inc. Huntsville, Alabama. These linkers optionally have amide linkages, sulfhydryl linkages, or heterofunctional linkages.

Tag binders are fixed to solid substrates using any of a variety of methods currently available. Solid substrates are commonly derivatized or functionalized by exposing all or a portion of the substrate to a chemical reagent which fixes a chemical group to the surface which is reactive with a portion of the tag binder. For example, groups which are suitable for attachment to a longer chain portion would include amines, hydroxyl, thiol, and carboxyl groups. Aminoalkylsilanes and hydroxyalkylsilanes can be used to functionalize a variety of surfaces, such as glass surfaces. The construction of such solid phase biopolymer arrays is well described in the literature. *See, e.g.,* Merrifield, *J. Am. Chem. Soc.* 85:2149-2154 (1963) (describing solid phase synthesis of, e.g., peptides); Geysen *et al., J. Immun. Meth.* 102:259-274 (1987) (describing synthesis of solid phase components on pins); Frank & Doring, *Tetrahedron* 44:60316040 (1988) (describing synthesis of various peptide sequences on cellulose disks); Fodor *et al., Science,* 251:767-777 (1991); Sheldon *et al., Clinical Chemistry* 39(4):718-719 (1993); and Kozal *et al., Nature Medicine* 2(7):753759 (1996) (all describing arrays of biopolymers fixed to solid substrates). Non-chemical approaches for fixing tag binders to substrates include other common methods, such as heat, cross-linking by UV radiation, and the like.

Antibodies to angiogenesis and tumorigenesis polypeptides

In addition to the detection of gene and gene expression using nucleic acid hybridization technology, one can also use immunoassays to detect proteins of the

invention. Such assays are useful for screening for modulators of angiogenesis, as well as for therapeutic and diagnostic applications. Immunoassays can be used to qualitatively or quantitatively analyze angiogenesis protein. A general overview of the applicable technology can be found in Harlow & Lane, *Antibodies: A Laboratory Manual* (1988).

5

A. Production of antibodies

Methods of producing polyclonal and monoclonal antibodies that react specifically with the angiogenesis proteins are known to those of skill in the art (*see, e.g.*, Coligan, *Current Protocols in Immunology* (1991); Harlow & Lane, *supra*; Goding,
10   *Monoclonal Antibodies: Principles and Practice* (2d ed. 1986); and Kohler & Milstein, *Nature* 256:495-497 (1975). Such techniques include antibody preparation by selection of antibodies from libraries of recombinant antibodies in phage or similar vectors, as well as preparation of polyclonal and monoclonal antibodies by immunizing rabbits or mice (*see, e.g.*, Huse *et al.*, *Science* 246:1275-1281 (1989); Ward *et al.*, *Nature* 341:544-546
15   (1989)).

A number of immunogens comprising portions of an angiogenesis protein may be used to produce antibodies specifically reactive with protein. For example, recombinant protein or an antigenic fragment thereof, can be isolated as described herein. Recombinant protein can be expressed in eukaryotic or prokaryotic cells as described
20   above, and purified as generally described above. Recombinant protein is the preferred immunogen for the production of monoclonal or polyclonal antibodies. Alternatively, a synthetic peptide derived from the sequences disclosed herein and conjugated to a carrier protein can be used an immunogen. Naturally occurring protein may also be used either in pure or impure form. The product is then injected into an animal capable of producing
25   antibodies. Either monoclonal or polyclonal antibodies may be generated, for subsequent use in immunoassays to measure the protein.

Methods of production of polyclonal antibodies are known to those of skill in the art. An inbred strain of mice (e.g., BALB/C mice) or rabbits is immunized with the protein using a standard adjuvant, such as Freund's adjuvant, and a standard
30   immunization protocol. The animal's immune response to the immunogen preparation is monitored by taking test bleeds and determining the titer of reactivity to the beta subunits. When appropriately high titers of antibody to the immunogen are obtained, blood is collected from the animal and antisera are prepared. Further fractionation of the antisera

to enrich for antibodies reactive to the protein can be done if desired (*see*, Harlow & Lane, *supra*).

Monoclonal antibodies may be obtained by various techniques familiar to those skilled in the art. Briefly, spleen cells from an animal immunized with a desired
5   antigen are immortalized, commonly by fusion with a myeloma cell (*see*, Kohler & Milstein, *Eur. J. Immunol.* 6:511-519 (1976)). Alternative methods of immortalization include transformation with Epstein Barr Virus, oncogenes, or retroviruses, or other methods well known in the art. Colonies arising from single immortalized cells are screened for production of antibodies of the desired specificity and affinity for the
10   antigen, and yield of the monoclonal antibodies produced by such cells may be enhanced by various techniques, including injection into the peritoneal cavity of a vertebrate host. Alternatively, one may isolate DNA sequences which encode a monoclonal antibody or a binding fragment thereof by screening a DNA library from human B cells according to the general protocol outlined by Huse, *et al.*, *Science* 246:1275-1281 (1989).

15   Monoclonal antibodies and polyclonal sera are collected and titered against the immunogen protein in an immunoassay, for example, a solid phase immunoassay with the immunogen immobilized on a solid support. Typically, polyclonal antisera with a titer of 10^4 or greater are selected and tested for their cross reactivity against non- angiogenesis proteins, using a competitive binding immunoassay. Specific
20   polyclonal antisera and monoclonal antibodies will usually bind with a K_d of at least about 0.1 mM, more usually at least about 1 μM, preferably at least about 0.1 μM or better, and most preferably, 0.01 μM or better. Antibodies specific only for a particular ortholog, such as a human ortholog, can also be made, by subtracting out other cross-reacting orthologs from a species such as a non-human mammal. In this manner,
25   antibodies that bind only to a desired protein may be obtained.

Once the specific antibodies against the protein are available, the protein can be detected by a variety of immunoassay methods. In addition, the antibody can be used therapeutically as modulators. For a review of immunological and immunoassay procedures, see *Basic and Clinical Immunology* (Stites & Terr eds., 7th ed. 1991).
30   Moreover, the immunoassays of the present invention can be performed in any of several configurations, which are reviewed extensively in Enzyme Immunoassay (Maggio, ed., 1980); and Harlow & Lane, *supra*.

B. Immunological binding assays

Protein can be detected and/or quantified using any of a number of well recognized immunological binding assays (*see, e.g.,* U.S. Patents 4,366,241; 4,376,110; 4,517,288; and 4,837,168). For a review of the general immunoassays, see also *Methods*

5   *in Cell Biology: Antibodies in Cell Biology*, volume 37 (Asai, ed. 1993); *Basic and Clinical Immunology* (Stites & Terr, eds., 7th ed. 1991). Immunological binding assays (or immunoassays) typically use an antibody that specifically binds to a protein or antigen of choice (in this case the protein or antigenic subsequence thereof). The antibody may be produced by any of a number of means well known to those of skill in the art and as

10   described above.

Immunoassays also often use a labeling agent to specifically bind to and label the complex formed by the antibody and antigen. The labeling agent may itself be one of the moieties comprising the antibody/antigen complex. Thus, the labeling agent may be a labeled protein or a labeled antibody. Alternatively, the labeling agent may be a

15   third moiety, such a secondary antibody, that specifically binds to the antibody/protein complex (a secondary antibody is typically specific to antibodies of the species from which the first antibody is derived). Other proteins capable of specifically binding immunoglobulin constant regions, such as protein A or protein G may also be used as the label agent. These proteins exhibit a strong non-immunogenic reactivity with

20   immunoglobulin constant regions from a variety of species (*see, e.g.,* Kronval *et al., J. Immunol.* 111:1401-1406 (1973); Akerstrom *et al., J. Immunol.* 135:2589-2542 (1985)). The labeling agent can be modified with a detectable moiety, such as biotin, to which another molecule can specifically bind, such as streptavidin. A variety of detectable moieties are well known to those skilled in the art.

25   Throughout the assays, incubation and/or washing steps may be required after each combination of reagents. Incubation steps can vary from about 5 seconds to several hours, optionally from about 5 minutes to about 24 hours. However, the incubation time will depend upon the assay format, antigen, volume of solution, concentrations, and the like. Usually, the assays will be carried out at ambient

30   temperature, although they can be conducted over a range of temperatures, such as 10°C to 40°C.

Non-competitive assay formats

Immunoassays for detecting protein in samples may be either competitive or noncompetitive. Noncompetitive immunoassays are assays in which the amount of antigen is directly measured. In one preferred "sandwich" assay, for example, the antibodies can be bound directly to a solid substrate on which they are immobilized. These immobilized antibodies then capture protein present in the test sample. Proteins thus immobilized are then bound by a labeling agent, such as a second antibody bearing a label. Alternatively, the second antibody may lack a label, but it may, in turn, be bound by a labeled third antibody specific to antibodies of the species from which the second antibody is derived. The second or third antibody is typically modified with a detectable moiety, such as biotin, to which another molecule specifically binds, e.g., streptavidin, to provide a detectable moiety.

Competitive assay formats

In competitive assays, the amount of protein present in the sample is measured indirectly by measuring the amount of a known, added (exogenous) protein displaced (competed away) from an antibody by the unknown protein present in a sample. In one competitive assay, a known amount of protein is added to a sample and the sample is then contacted with an antibody that specifically binds to protein. The amount of exogenous protein bound to the antibody is inversely proportional to the concentration of protein present in the sample. In a particularly preferred embodiment, the antibody is immobilized on a solid substrate. The amount of protein bound to the antibody may be determined either by measuring the amount of protein present in protein/antibody complex, or alternatively by measuring the amount of remaining uncomplexed protein. The amount of protein may be detected by providing a labeled molecule.

A hapten inhibition assay is another preferred competitive assay. In this assay the known protein is immobilized on a solid substrate. A known amount of antibody is added to the sample, and the sample is then contacted with the immobilized protein. The amount of antibody bound to the known immobilized protein is inversely proportional to the amount of protein present in the sample. Again, the amount of immobilized antibody may be detected by detecting either the immobilized fraction of antibody or the fraction of the antibody that remains in solution. Detection may be direct where the antibody is labeled or indirect by the subsequent addition of a labeled moiety that specifically binds to the antibody as described above.

Cross-reactivity determinations

Immunoassays in the competitive binding format can also be used for crossreactivity determinations. For example, a protein can be immobilized to a solid support. Proteins are added to the assay that compete for binding of the antisera to the immobilized antigen. The ability of the added proteins to compete for binding of the antisera to the immobilized protein is compared to the ability of the protein to compete with itself. The percent crossreactivity for the above proteins is calculated, using standard calculations. Those antisera with less than 10% crossreactivity with each of the added proteins listed above are selected and pooled. The cross-reacting antibodies are optionally removed from the pooled antisera by immunoabsorption with the added considered proteins, e.g., distantly related homologs.

The immunoabsorbed and pooled antisera are then used in a competitive binding immunoassay as described above to compare a second protein, thought to be perhaps an allele or polymorphic variant of a protein, to the immunogen protein. In order to make this comparison, the two proteins are each assayed at a wide range of concentrations and the amount of each protein required to inhibit 50% of the binding of the antisera to the immobilized protein is determined. If the amount of the second protein required to inhibit 50% of binding is less than 10 times the amount of the protein that is required to inhibit 50% of binding, then the second protein is said to specifically bind to the polyclonal antibodies generated to the immunogen.

Other assay formats

Western blot (immunoblot) analysis is used to detect and quantify the presence of protein in the sample. The technique generally comprises separating sample proteins by gel electrophoresis on the basis of molecular weight, transferring the separated proteins to a suitable solid support, (such as a nitrocellulose filter, a nylon filter, or derivatized nylon filter), and incubating the sample with the antibodies that specifically bind the protein. The antibodies specifically bind to the protein on the solid support. These antibodies may be directly labeled or alternatively may be subsequently detected using labeled antibodies (e.g., labeled sheep anti-mouse antibodies) that specifically bind to the antibodies.

Other assay formats include liposome immunoassays (LIA), which use liposomes designed to bind specific molecules (e.g., antibodies) and release encapsulated

reagents or markers. The released chemicals are then detected according to standard techniques (*see* Monroe *et al.*, *Amer. Clin. Prod. Rev.* 5:34-41 (1986)).

Reduction of non-specific binding

One of skill in the art will appreciate that it is often desirable to minimize non-specific binding in immunoassays. Particularly, where the assay involves an antigen or antibody immobilized on a solid substrate it is desirable to minimize the amount of non-specific binding to the substrate. Means of reducing such non-specific binding are well known to those of skill in the art. Typically, this technique involves coating the substrate with a proteinaceous composition. In particular, protein compositions such as bovine serum albumin (BSA), nonfat powdered milk, and gelatin are widely used with powdered milk being most preferred.

Labels

The particular label or detectable group used in the assay is not a critical aspect of the invention, as long as it does not significantly interfere with the specific binding of the antibody used in the assay. The detectable group can be any material having a detectable physical or chemical property. Such detectable labels have been well-developed in the field of immunoassays and, in general, most any label useful in such methods can be applied to the present invention. Thus, a label is any composition detectable by spectroscopic, photochemical, biochemical, immunochemical, electrical, optical or chemical means. Useful labels in the present invention include magnetic beads (e.g., DYNABEADS™), fluorescent dyes (e.g., fluorescein isothiocyanate, Texas red, rhodamine, and the like), radiolabels (e.g., ^{3}H, ^{125}I, ^{35}S, ^{14}C, or ^{32}P), enzymes (e.g., horse radish peroxidase, alkaline phosphatase and others commonly used in an ELISA), and colorimetric labels such as colloidal gold or colored glass or plastic beads (e.g., polystyrene, polypropylene, latex, etc.).

The label may be coupled directly or indirectly to the desired component of the assay according to methods well known in the art. As indicated above, a wide variety of labels may be used, with the choice of label depending on sensitivity required, ease of conjugation with the compound, stability requirements, available instrumentation, and disposal provisions.

Non-radioactive labels are often attached by indirect means. Generally, a ligand molecule (e.g., biotin) is covalently bound to the molecule. The ligand then binds

to another molecules (e.g., streptavidin) molecule, which is either inherently detectable or covalently bound to a signal system, such as a detectable enzyme, a fluorescent compound, or a chemiluminescent compound. The ligands and their targets can be used in any suitable combination with antibodies that recognize the protein, or secondary

5   antibodies.

The molecules can also be conjugated directly to signal generating compounds, e.g., by conjugation with an enzyme or fluorophore. Enzymes of interest as labels will primarily be hydrolases, particularly phosphatases, esterases and glycosidases, or oxidotases, particularly peroxidases. Fluorescent compounds include fluorescein and

10   its derivatives, rhodamine and its derivatives, dansyl, umbelliferone, etc. Chemiluminescent compounds include luciferin, and 2,3-dihydrophthalazinediones, e.g., luminol. For a review of various labeling or signal producing systems that may be used, see U.S. Patent No. 4,391,904.

Means of detecting labels are well known to those of skill in the art. Thus,

15   for example, where the label is a radioactive label, means for detection include a scintillation counter or photographic film as in autoradiography. Where the label is a fluorescent label, it may be detected by exciting the fluorochrome with the appropriate wavelength of light and detecting the resulting fluorescence. The fluorescence may be detected visually, by means of photographic film, by the use of electronic detectors such

20   as charge coupled devices (CCDs) or photomultipliers and the like. Similarly, enzymatic labels may be detected by providing the appropriate substrates for the enzyme and detecting the resulting reaction product. Finally simple colorimetric labels may be detected simply by observing the color associated with the label. Thus, in various dipstick assays, conjugated gold often appears pink, while various conjugated beads

25   appear the color of the bead.

Some assay formats do not require the use of labeled components. For instance, agglutination assays can be used to detect the presence of the target antibodies. In this case, antigen-coated particles are agglutinated by samples comprising the target antibodies. In this format, none of the components need be labeled and the presence of

30   the target antibody is detected by simple visual inspection.

Gene therapy

The present invention provides the nucleic acids of angiogenesis or tumorigenesis associated protein for the transfection of cells *in vitro* and *in vivo*. These

nucleic acids can be inserted into any of a number of well-known vectors for the transfection of target cells and organisms as described below. The nucleic acids are transfected into cells, *ex vivo* or *in vivo*, through the interaction of the vector and the target cell. The nucleic acid, under the control of a promoter, then expresses a protein of

5 the present invention, thereby mitigating the effects of absent, partial inactivation, or abnormal expression of the angiogenesis or tumorigenesis gene, particularly as it relates to angiogenesis. The compositions are administered to a patient in an amount sufficient to elicit a therapeutic response in the patient. An amount adequate to accomplish this is defined as "therapeutically effective dose or amount."

10 Such gene therapy procedures have been used to correct acquired and inherited genetic defects, cancer, and other diseases in a number of contexts. The ability to express artificial genes in humans facilitates the prevention and/or cure of many important human diseases, including many diseases which are not amenable to treatment by other therapies (for a review of gene therapy procedures, *see* Anderson, *Science*

15 256:808-813 (1992); Nabel & Felgner, TIBTECH 11:211-217 (1993); Mitani & Caskey, TIBTECH 11:162-166 (1993); Mulligan, *Science* 926-932 (1993); Dillon, TIBTECH 11:167-175 (1993); Miller, *Nature* 357:455-460 (1992); Van Brunt, *Biotechnology* 6(10):1149-1154 (1998); Vigne, *Restorative Neurology and Neuroscience* 8:35-36 (1995); Kremer & Perricaudet, *British Medical Bulletin* 51(1):31-44 (1995); Haddada *et*

20 *al.,* in *Current Topics in Microbiology and Immunology* (Doerfler & Böhm eds., 1995); and Yu *et al., Gene Therapy* 1:13-26 (1994)).

The nucleic acids of the invention can also be used to make transgenic animals, such as transgenic mice, either by knock-out or overexpression. Such animals are useful, e.g., for testing modulators of angiogenesis and tumorigenesis.

25

Pharmaceutical compositions and administration

Pharmaceutically acceptable carriers are determined in part by the particular composition being administered (e.g., nucleic acid, protein, modulatory compounds or transduced cell), as well as by the particular method used to administer the

30 composition. Accordingly, there are a wide variety of suitable formulations of pharmaceutical compositions of the present invention (*see, e.g., Remington's Pharmaceutical Sciences*, 17th ed., 1989). Administration can be in any convenient manner, e.g., by injection, oral administration, inhalation, transdermal application, or rectal administration.

Formulations suitable for oral administration can consist of (a) liquid solutions, such as an effective amount of the packaged nucleic acid suspended in diluents, such as water, saline or PEG 400; (b) capsules, sachets or tablets, each containing a predetermined amount of the active ingredient, as liquids, solids, granules or gelatin; (c) suspensions in an appropriate liquid; and (d) suitable emulsions. Tablet forms can include one or more of lactose, sucrose, mannitol, sorbitol, calcium phosphates, corn starch, potato starch, microcrystalline cellulose, gelatin, colloidal silicon dioxide, talc, magnesium stearate, stearic acid, and other excipients, colorants, fillers, binders, diluents, buffering agents, moistening agents, preservatives, flavoring agents, dyes, disintegrating agents, and pharmaceutically compatible carriers. Lozenge forms can comprise the active ingredient in a flavor, e.g., sucrose, as well as pastilles comprising the active ingredient in an inert base, such as gelatin and glycerin or sucrose and acacia emulsions, gels, and the like containing, in addition to the active ingredient, carriers known in the art.

The compound of choice, alone or in combination with other suitable components, can be made into aerosol formulations (i.e., they can be "nebulized") to be administered via inhalation. Aerosol formulations can be placed into pressurized acceptable propellants, such as dichlorodifluoromethane, propane, nitrogen, and the like.

Formulations suitable for parenteral administration, such as, for example, by intraarticular (in the joints), intravenous, intramuscular, intradermal, intraperitoneal, and subcutaneous routes, include aqueous and non-aqueous, isotonic sterile injection solutions, which can contain antioxidants, buffers, bacteriostats, and solutes that render the formulation isotonic with the blood of the intended recipient, and aqueous and non-aqueous sterile suspensions that can include suspending agents, solubilizers, thickening agents, stabilizers, and preservatives. In the practice of this invention, compositions can be administered, for example, by intravenous infusion, orally, topically, intraperitoneally, intravesically or intrathecally. Parenteral administration and intravenous administration are the preferred methods of administration. The formulations of commends can be presented in unit-dose or multi-dose sealed containers, such as ampules and vials.

Injection solutions and suspensions can be prepared from sterile powders, granules, and tablets of the kind previously described. Cells transduced by nucleic acids for *ex vivo* therapy can also be administered intravenously or parenterally as described above.

The dose administered to a patient, in the context of the present invention should be sufficient to effect a beneficial therapeutic response in the patient over time.

The dose will be determined by the efficacy of the particular vector employed and the condition of the patient, as well as the body weight or surface area of the patient to be treated. The size of the dose also will be determined by the existence, nature, and extent of any adverse side-effects that accompany the administration of a particular vector, or transduced cell type in a particular patient.

In determining the effective amount of the vector to be administered in the treatment or prophylaxis of conditions owing to diminished or aberrant expression of the angiogenesis protein, the physician evaluates circulating plasma levels of the vector, vector toxicities, progression of the disease, and the production of anti-vector antibodies. In general, the dose equivalent of a naked nucleic acid from a vector is from about 1 μg to 100 μg for a typical 70 kilogram patient, and doses of vectors which include a retroviral particle are calculated to yield an equivalent amount of therapeutic nucleic acid.

For administration, compounds and transduced cells of the present invention can be administered at a rate determined by the LD-50 of the inhibitor, vector, or transduced cell type, and the side-effects of the inhibitor, vector or cell type at various concentrations, as applied to the mass and overall health of the patient. Administration can be accomplished via single or divided doses.

EXAMPLES

The following examples are offered to illustrate, but not to limit the claimed invention.

Example 1: Identification of genes involved in modulation of angiogenesis and tumorigenesis *in vitro*

Using a retroviral base system, , complex libraries of cDNAs and GFP-fusions have been expressed in human primary endothelial cells (e.g., HUVECS). Cells that switch to a differentiated angiostatic state can be identified. The cells are then assayed for migration along a haptotactic gradient of specific matrix proteins such as vitronectin and fibronectin in a Boyden chamber assay. Cells were selected for impaired haptotaxis (*see, e.g.,* Klemke *et al., J. Cell Biol.* 4:961-972 (1998)).

Example 2: Identification of genes involved in modulation of angiogenesis and tumorigenesis *in vivo*

This study in mice was designed to provide information on the growth and angiogenic characteristics of MDA-MB-231 infected with either EFS-U6TO-Ax14 vector

5   or EFS-U6TO-FF1 (isogenic negative control) and implanted subcutaneously in mice (Strain:CB-17 scid). MDA-MB-231 (wt) cells will also be implanted and measured. Tumor Cell Injection Density: 1 X 107 per injection site (shaved right hind flank).

When tumors reach a diameter of approximately 1 cm, animals are randomly divided into subgroups according to tumor size using a stratified randomization

10   method (Day 0). Tumors in selected subgroups are resected by survival surgery and fixed in formalin and the animals will be observed for signs of metastasis via changes in body weight and/or clinical signs. Animals showing any of these signs in severity are terminated and the lungs, liver, sternum, femur, and lymph nodes (axial and mesenteric) are harvested and fixed in 10% buffered formalin for histological examination. Tumors

15   in remaining subgroups will continue to be measured until they reach 2,000mm3.

The mean tumor volume for each group was calculated for each time point. Comparisons between groups at specific times are made using an unpaired, two-tailed t-test, and the results analyzed using analysis of variance (ANOVA) or the student's t-test. Differentials in tumor growth between groups are determined by calculating

20   volume-doubling time (VDT), or by determining the survival time.

It is understood that the examples and embodiments described herein are for illustrative purposes only and that various modifications or changes in light thereof will be suggested to persons skilled in the art and are to be included within the spirit and

25   purview of this application and scope of the appended claims. All publications, patents, and patent applications cited herein are hereby incorporated by reference in their entirety for all purposes.

SEQUENCE LISTING

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60
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>gi|21536468|ref|NP_001690.2| AXL receptor tyrosine kinase isoform 2;
AXL transforming sequence/gene; oncogene AXL [Homo sapiens]
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Tubulin cofactor D

GH1-13-PCR-G3F1
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>gi|8400735|ref|NM_005993.2| Homo sapiens tubulin-specific chaperone d
(TBCD), mRNA
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TACCAAG

>gi|8400736|ref|NP_005984.2| beta-tubulin cofactor D [Homo sapiens]
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Transglutaminase 2

GH1-173-PCR-G3F1
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gi|20141877|sp|P21980|TGM2_HUMAN Protein-glutamine gamma-
glutamyltransferase (Tissue transglutaminase) (TGase C) (TGC) (TG(C))
(Tranglutaminase 2) (TGase-H)
MAEELVLERCDLELETNGRDHHTADLCREKLVVRRGQPFWLTLHFEGRNYEASVDSLTFSVVTGPAPSQE
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>gi|4759227|ref|NM_004613.1| Homo sapiens transglutaminase 2 (C
polypeptide, protein-glutamine-gamma-glutamyltransferase) (TGM2), mRNA
AACAGGCGTGACGCCAGTTCTAAACTTGAAACAAAACAAAACTTCAAAGTACACCAAAATAGAACCTCCT
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>gi|4759228|ref|NP_004604.1| transglutaminase 2 (C polypeptide, protein-
glutamine-gamma-glutamyltransferase) [Homo sapiens]
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EEQKTVEIPDPVEAGEEVKVRMDLVPLHMGLHKLVVNFESDKLKAVKGFRNVIIGPA

>gi|13097680|gb|BC003551.1|BC003551 Homo sapiens, Similar to
transglutaminase 2 (C polypeptide, protein-glutamine-gamma-
glutamyltransferase), clone MGC:1193 IMAGE:3544757, mRNA, complete cds
CTCCGCCTCGGCAGTGCCAGCCGCCAGTGGTCGCACTTGGAGGGTCTCGCCGCCAGTGGAAGGAGCCACC
GCCCCGCCCGACCATGGCCGAGGAGCTGGTCTTAGAGAGGTGTGATCTGGAGCTGGAGACCAATGGCCG
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CAACTACAACTCGGCCCATGACCAGAACAGCAACCTTCTCATCGAGTACTTCCGCAATGAGTTTGGGGAG
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TAGGTAGTGACCTAAAAAAAAAAAAAAAAAAAA

>gi|13097681|gb|AAH03551.1|AAH03551 Similar to transglutaminase 2 (C
polypeptide, protein-glutamine-gamma-glutamyltransferase) [Homo sapiens]
MAEELVLERCDLELETNGRDHHTADLCREKLVVRRGQPFWLTLHFEGRNYEASVDSLTFSVVTGPAPSQE
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>gi|339577|gb|M98478.1|HUMTGH1A Human transglutaminase mRNA, complete
cds
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>gi|339578|gb|AAA36739.1| transglutaminase
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Cytosine deaminase

GH1-27-PCR-G3F1
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TGTCATCTGCTGCGATCCGGCAG

>gi|23503055|sp|P32321|DCTD_HUMAN Deoxycytidylate deaminase (dCMP
deaminase)
MSEVSCKKRDDYLEWPEYFMAVAFLSAQRSKDPNSQVGACIVNSENKIVGIGYNGMPNGCSDDVLPWRRT
AENKLDTKYPYVCHAELNAIMNKNSTDVKGCSMYVALFPCNECAKLIIQAGIKEVIFMSDKYHDSDEATA
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>gi|4503276|ref|NM_001921.1| Homo sapiens dCMP deaminase (DCTD), mRNA
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TATTAAAATCT

>gi|4503277|ref|NP_001912.1| dCMP deaminase [Homo sapiens]
MSEVSCKKRDDYLEWPEYFMAVAFLSAQRSKDPNSQVGACIVNSENKIVGIGYNGMPNGCSDDVLPWRRT
AENKLDTKYPYVCHAELNAIMNKNSTDVKGCSMYVALFPCNECAKLIIQAGIKEVIFTSDKYHDSDEATA
ARLLFNMAGVTFRKFIPKCSKIVIDFDSINSRPSQKLQ

Peptidase M41 (Paraplegin)

GH1-40-PCR-G3F1
GTGGAAATGCCCTGTTACTCTGTGGGGATGACGGCAGTGGGCCTGGCCATCCTGTGGTATGTTTTCCGTCTG
GCCGGGATGACTGGAAGGGAAGGTGGATTCAGTGCTTTTAATCAGCTTAAAATGGCTCGTTTCACCATTGTG
GATTGGAAGATGGGGAAAGGGAGTCAGCTTCAAAGACGTGGCAGGAATGCACGAAGCCAAACTGGAAGTCCG
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CTGGCGATGCCGGCCCAGAGTTCGTGGAGGTCATTGGAGGCCTCGGCGCTCCCGTGTGCGGAGCCTCTTTAA
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ACCATGTCCGGCTTCTCCAACACNGAGGAGGAGCAGACGCTCAACCAGCTTCTGGTNAGAAATGGATGGAAA
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>gi|4507172|ref|NM_003119.1| Homo sapiens spastic paraplegia 7,
paraplegin (pure and complicated autosomal recessive) (SPG7), mRNA
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CD13 Aminopeptidase

GH1-72-PCR-G3F1
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>gi|113743|sp|P15144|AMPN_HUMAN Aminopeptidase N (Microsomal
aminopeptidase) (GP150) (Myeloid plasma membrane glycoprotein CD13)
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>gi|4502094|ref|NM_001150.1| Homo sapiens alanyl (membrane)
aminopeptidase (aminopeptidase N, aminopeptidase M, microsomal
aminopeptidase, CD13, p150) (ANPEP), mRNA

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>gi|4502095|ref|NP_001141.1| membrane alanine aminopeptidase precursor;
microsomal aminopeptidase; Alanyl (membrane) aminopeptidase
(aminopeptidase N, aminopeptidase M, [Homo sapiens]

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PRK-1

GH1-54-PCR-G3F1
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>gi|4506072|ref|NM_002741.1| Homo sapiens protein kinase C-like 1
(PRKCL1), mRNA
```
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TTGGCCCGGCGCCTGCCACCGCCCTTTGTGCCCACGCTGTCCGGCCGCACCGACGTCAGCAACTTCGACG
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>gi|4506073|ref|NP_002732.1| protein kinase C-like 1; serine-threonine
kinase N [Homo sapiens]
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Zip kinase

GH1-68-PCR-G3F1
GCTGGGTTTCATTTCGAGTATTCGCGGGCCTGCTCTCAGCTAGGTTTAGCCCGTTCGTGACCCTCCACGTGC
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>gi|4557510|ref|NM_001348.1| Homo sapiens death-associated protein
kinase 3 (DAPK3), mRNA
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CAGAT
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>gi|4557511|ref|NP_001339.1| death-associated protein kinase 3 [Homo sapiens]
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>gi|2911155|dbj|AB007144.1| Homo sapiens mRNA for ZIP-kinase, complete cds
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>gi|2911156|dbj|BAA24955.1| ZIP-kinase [Homo sapiens]
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```

>gi|5162883|dbj|AB022341.1| Homo sapiens mRNA for ZIP kinase, complete cds

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>gi|5162884|dbj|BAA81746.1| ZIP kinase [Homo sapiens]
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Gas6

GH1-50-PCR-G3F1
GCGCAGGAATCTGGTCATCAAGGTCAACAGGGATGCTGTCATGAAAATCGCGGTGGCCGGGGACTTGTTCCA
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>gi|4557616|ref|NM_000820.1| Homo sapiens growth arrest-specific 6
(GAS6), mRNA
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>gi|4557617|ref|NP_000811.1| growth arrest-specific 6; AXL stimulatory
factor [Homo sapiens]
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SRm160

GH1-67-PCR-G3F1
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>gi|19923465|ref|NM_016333.2| Homo sapiens serine/arginine repetitive
matrix 2 (SRRM2), mRNA
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[Homo sapiens]

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Non-muscle myosin heavy chain

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>gi|22507396|ref|NM_002473.2| Homo sapiens myosin, heavy polypeptide 9,
non-muscle (MYH9), mRNA
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Calmodulin 2

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>gi|13477324|gb|BC005137.1|BC005137 Homo sapiens, calmodulin 2
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complete cds
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Novel Symporter

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Novel Semaphorin

GH1-204-PCR-G3F1
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Novel Zn finger helicase

GH1-31-PCR-G3F1
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Novel Sugar transporter

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human Plexin-A2

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deoxycytidylate deaminase

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